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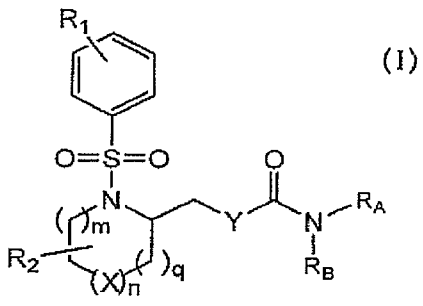
(54) Title: ARYL SULFONYL HETEROCYCLES



(I)

(57) Abstract: Compounds of Formula (I) are provided in which the variables are as described herein. Such compounds may be used to modulate bradykinin receptor activity *in vivo* or *in vitro*, and are particularly useful in the treatment of conditions responsive to B_1 modulation in humans, domesticated companion animals and livestock animals, including inflammation and pain. Pharmaceutical compositions and methods for using them to treat such disorders are provided, as are methods for using such ligands for receptor localization studies and various *in vitro* assays.

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ARYL SULFONYL HETEROCYCLES

FIELD OF THE INVENTION

This invention relates generally to aryl sulfonyl heterocycles, and to the use of such compounds to treat conditions responsive to bradykinin receptor-1 (B_1) modulation. The invention further relates to the use of such compounds as reagents for the identification of other agents that bind to B_1, and as probes for the detection and localization of B_1.

BACKGROUND OF THE INVENTION

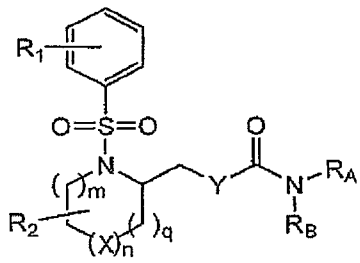
Millions of people throughout the world are incapacitated by pain. Existing treatments for pain are, unfortunately, not completely effective, and typically have undesirable side effects. Non-steroidal anti-inflammatory drugs are only moderately effective against pain, and have serious renal and gastrointestinal side effects at high doses. Opiates, such as morphine, are potent analgesics, but their usefulness is limited because of adverse side effects, such as physical addictiveness and withdrawal properties, as well as respiratory depression, mood changes, and decreased intestinal motility with concomitant constipation, nausea, vomiting, and alterations in the endocrine and autonomic nervous systems. There is thus a need for effective agents for the treatment of pain.

Bradykinin (BK) is a nonapeptide that functions in cardiovascular homeostasis, contraction and relaxation of smooth muscles, inflammation and pain. The effects of BK are mediated by specific G protein-coupled BK receptors, of which there are at least two distinct subtypes termed B_1 and B_2. The B_2 receptor is expressed constitutively in a variety of tissues. In contrast, the B_1 receptor is inducibly expressed in response to pathophysiological conditions such as inflammation, pain, trauma, bacterial infection, burns and shock. Accordingly, B_1 is a particularly attractive drug target for these and other conditions, and agents that act at this receptor may be targeted specifically to injured tissues, with minimal effects in normal tissues. In addition, compounds that bind to B_1 and/or modulate the activity of B_1 also find use as research tools.

There is thus a need in the art for small molecule modulators of B_1 activity. The present invention fulfills this need and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides aryl sulfonyl heterocycles that satisfy Formula I, or are a pharmaceutically acceptable salt, solvate or ester of such a compound:



Formula I

Within Formula I:

n is 0 or 1;

if n is 0, then m is 1 and q is 0 or 1;

if n is 1, then either (i) m is 1 and q is 1 or 2 or (i) q is 1 and m is 1 or 2;

X is NR_3, O, S, SO or SO_2;

Y is -O-CH_2-, -N(R_{10})-CH_2-, -CH_2-CH_2-, -CH=CH-, -CH_2-O-CH_2-, -CH_2-CH_2-CH_2- or -O-CH_2-CH_2-;

R_1 represents from 0 to 5 ring substituents; preferably such substituents are independently chosen from:

(i) halogen, hydroxy, cyano, amino, nitro, aminocarbonyl, aminosulfonyl and –COOH;

(ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylsulfonylC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminosulfonylC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminocarbonylC_0-C_4alkyl, and (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from halogen, hydroxy, cyano and amino; and

(iii) groups that are taken together to form a fused carbocyclic ring that is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl;

R_2 represents from 0 to 4 substituents; preferably any such substituents are independently chosen from oxo, hydroxy and C_1-C_8alkyl;

R_3 is hydrogen or a substituent such as C_1-C_8alkyl or C_1-C_8alkanoyl;

R_{10} is hydrogen or a substituent such as C_1-C_4alkyl;

R_A is hydrogen or a substituent such as C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, or mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, each of which is optionally substituted with hydroxy, amino or oxo; and

R_B is a substituent such as C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, or (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl, each of which is optionally substituted and each of which is preferably substituted with from 0 to 6 substituents independently chosen from:

(i) amino, halogen, hydroxy, cyano and oxo; and

(ii) C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, phenylC_0-C_4alkyl and (5- or 6-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 4 substituents

independently chosen from amino, cyano, halogen, hydroxy, C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, mono- or di-(C_1-C_6alkyl)amino, phenylC_0-C_4alkyl and phenylC_0-C_4alkoxy;

or R_A and R_B are taken together to form a 4- to 7-membered heterocycloalkyl that is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from:

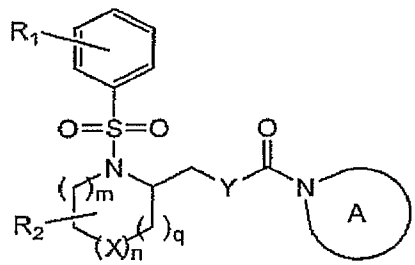
(i) hydroxy, oxo, cyano and amino; and

(ii) C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl; and

(iii) substituents that are taken together to form a spiro C_4-C_{10}carbocycle or a spiro 4- to 10-membered heterocycle;

each of which (ii) and (iii) is optionally substituted and is preferably substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl.

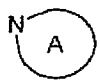
Within further aspects, aryl sulfonyl heterocycles of Formula I further satisfy Formula II:



Formula II

or are a pharmaceutically acceptable salt, solvate or ester of such a compound.

Within Formula II:



represents a 4- to 7-membered, N-linked heterocycloalkyl that is optionally substituted and is preferably substituted with from 0 to 4 substituents independently chosen from:

(i) hydroxy, oxo, cyano and amino;

(ii) C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl; and

(iii) substituents that are taken together to form a spiro C_4-C_{10}carbocycle or a spiro 4- to 10-membered heterocycle;

each of which (ii) and (iii) is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl;

and the remaining variables are as described for Formula I.

Within certain aspects, aryl sulfonyl heterocycles of Formula I, and other Formulas provided herein, are B_1 modulators and exhibit a K_i of no greater than 5 micromolar, 2 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in the B_1 binding assay

provided in Example 6, herein, and/or have an EC_{50} or IC_{50} value of no greater than 5 micromolar, 2 micromolar, 1 micromolar, 500 nanomolar, 100 nanomolar, 50 nanomolar or 10 nanomolar in an assay for determination of B_1 agonist or antagonist activity as provided in Example 7, herein.

In certain embodiments, aryl sulfonyl heterocycles of Formula I are B_1 antagonists; preferably such antagonists exhibit no detectable B_1 agonist activity.

Within certain aspects, aryl sulfonyl heterocycles of Formula I are labeled with a detectable marker (*e.g.*, radiolabeled or fluorescein conjugated).

The present invention further provides, within other aspects, pharmaceutical compositions comprising at least one aryl sulfonyl heterocycle of Formula I in combination with a physiologically acceptable carrier or excipient.

Methods are further provided for inhibiting agonist-induced B_1 activity. Within certain such aspects, the inhibition takes place *in vitro*. Such methods comprise contacting a B_1 receptor with at least one B_1 antagonist as described herein, under conditions and in an amount or concentration sufficient to detectably inhibit agonist-induced B_1 activity. Within other such aspects, the B_1 receptor is in a patient. Such methods comprise contacting cells expressing a B_1 receptor in a patient with at least one B_1 antagonist as described herein in an amount or concentration that would be sufficient to detectably inhibit agonist-induced B_1 activity in cells expressing a cloned B_1 receptor *in vitro*.

The present invention further provides methods for treating a condition responsive to B_1 receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one aryl sulfonyl heterocycle of Formula I.

Within other aspects, methods are provided for treating pain in a patient, comprising administering to a patient suffering from (or at risk for) pain a therapeutically effective amount of at least one aryl sulfonyl heterocycle of Formula I. Pain conditions that may be treated include, but are not limited to, inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain, and pain associated with osteoarthritis or trauma.

Within further aspects, the present invention provides methods for determining the presence or absence of B_1 in a sample, comprising: (a) contacting a sample with an aryl sulfonyl heterocycle of Formula I under conditions that permit binding of the compound to B_1; and (b) detecting a signal indicative of a level of the compound bound to B_1.

In yet another aspect, the present invention provides methods of preparing the compounds disclosed herein, including the intermediates.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

As noted above, the present invention provides aryl sulfonyl heterocycles. Such compounds may be used *in vitro* or *in vivo* in a variety of contexts, as described herein.

TERMINOLOGY

Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. If a compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, X, R_A, q). Unless otherwise specified, each variable within such a formula is defined independently of any other variable, and any variable that occurs more than one time in a formula is defined independently at each occurrence.

The term "aryl sulfonyl heterocycles" encompasses all compounds of Formula I, and includes pharmaceutically acceptable salts, solvates and esters of such compounds.

A "pharmaceutically acceptable salt" of a compound recited herein is an acid or base salt that is suitable for use in contact with the tissues of human beings or animals without excessive toxicity or carcinogenicity, and preferably without irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutically acceptable anions for use in salt formation include, but are not limited to, acetate, 2-acetoxybenzoate, ascorbate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, diphosphate, edetate, estolate (ethylsuccinate), formate, fumarate, gluceptate, gluconate, glutamate, glycolate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroiodide, hydroxymaleate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phenylacetate, phosphate, polygalacturonate, propionate, salicylate, stearate, subacetate, succinate, sulfamate, sulfanilate, sulfate, sulfonates including besylate (benzenesulfonate), camsylate (camphorsulfonate), edisylate (ethane-1,2-disulfonate), esylate (ethanesulfonate) 2-hydroxyethylsulfonate, mesylate (methanesulfonate), triflate (trifluoromethanesulfonate) and tosylate (*p*-toluenesulfonate), tannate, tartrate, teoclate and triethiodide. Similarly, pharmaceutically acceptable cations for use in salt formation include, but are not limited to ammonium, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, and metals such as aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein. In general, a pharmaceutically acceptable acid or base salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic

solvent, or in a mixture of the two; generally, the use of nonaqueous media, such as ether, ethyl acetate, ethanol, methanol, isopropanol or acetonitrile, is preferred.

It will be apparent that each compound provided herein may, but need not, be formulated as a solvate (*e.g.*, a hydrate) or non-covalent complex. In addition, the various crystal forms and polymorphs are within the scope of the present invention. Also provided herein are prodrugs of the compounds provided herein. A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a compound provided herein. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxy, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, phosphate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein. Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved *in vivo* to yield the parent compounds.

As used herein, the term "alkyl" refers to a straight or branched chain saturated aliphatic hydrocarbon. Alkyl groups include groups having from 1 to 8 carbon atoms (C_1-C_8alkyl), from 1 to 6 carbon atoms (C_1-C_6alkyl) and from 1 to 4 carbon atoms (C_1-C_4alkyl), such as methyl, ethyl, propyl, isopropyl, n-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl or 3-methylpentyl. "C_0-C_4alkyl" refers to a single covalent bond (C_0) or an alkylene group having 1, 2, 3 or 4 carbon atoms; "C_0-C_6alkyl" refers to a single covalent bond or a C_1-C_6alkylene group..

"Alkylene" refers to a divalent alkyl group, as defined above. C_1-C_4alkylene is an alkylene group having 1, 2, 3 or 4 carbon atoms.

"Alkenyl" refers to straight or branched chain alkene groups, which comprise at least one unsaturated carbon-carbon double bond. Alkenyl groups include C_2-C_8alkenyl, C_2-C_6alkenyl and C_2-C_4alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have one or more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C_2-C_8alkynyl, C_2-C_6alkynyl and C_2-C_4alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

A "cycloalkyl" is a saturated or partially saturated cyclic group in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and partially saturated variants thereof. Certain cycloalkyl groups are C_3-C_8cycloalkyl, in which the ring contains from 3 to 8 ring members, all of which are carbon. A "(C_3-C_8cycloalkyl)C_0-C_4alkyl" is a C_3-C_8cycloalkyl group linked via a single covalent bond or a C_1-C_4alkylene group.

By "alkoxy," as used herein, is meant an alkyl group attached via an oxygen bridge. Alkoxy groups include C_1-C_6alkoxy and C_1-C_4alkoxy groups, which have from 1 to 6 or from 1 to 4 carbon

atoms, respectively. Methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy are representative alkoxy groups.

Similarly, "alkylthio" refers to an alkyl group as attached via a sulfur bridge (*i.e.*, –S–alkyl). Alkylthio groups include C_1-C_6alkylthio and C_1-C_4alkylthio groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

The term "oxo," as used herein refers to an oxygen substituent of a carbon atom that results in the formation of a carbonyl group (C=O). An oxo group that is a substituent of a nonaromatic carbon atom results in a conversion of $–CH_2–$ to –C(=O)–. An oxo group that is a substituent of an aromatic carbon atom results in a conversion of –CH– to –C(=O)– and may result in a loss of aromaticity.

"Alkylsulfinyl" refers to groups of the formula –(SO)–alkyl, in which the sulfur atom is the point of attachment. Alkylsulfinyl groups include C_1-C_6alkylsulfinyl and C_1-C_4alkylsulfinyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

"Alkylsulfonyl" refers to groups of the formula $–(SO_2)–$alkyl, in which the sulfur atom is the point of attachment. Alkylsulfonyl groups include C_1-C_6alkylsulfonyl and C_1-C_4alkylsulfonyl groups, which have from 1 to 6 or from 1 to 4 carbon atoms, respectively.

The term "alkanoyl" refers to an acyl group (*e.g.*, –(C=O)–alkyl), in which carbon atoms are in a linear or branched alkyl arrangement and where attachment is through the carbon of the keto group. Alkanoyl groups have the indicated number of carbon atoms, with the carbon of the keto group being included in the numbered carbon atoms. For example a C_2alkanoyl group is an acetyl group having the formula $-(C=O)CH_3$; "C_1alkanoyl" refers to –(C=O)H. Alkanoyl groups include, for example, C_1-C_8alkanoyl, C_1-C_6alkanoyl and C_1-C_4alkanoyl groups, which have from 1 to 8, from 1 to 6 or from 1 to 4 carbon atoms, respectively.

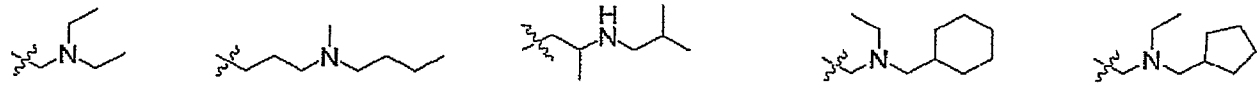
Similarly, "alkyl ether" refers to a linear or branched ether substituent. Alkyl ether groups include C_2-C_8alkyl ether, C_2-C_6alkyl ether and C_2-C_4alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively. A C_2alkyl ether has the structure $–CH_2–O–CH_3$.

The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*i.e.*, a group having the general structure –C(=O)–O–alkyl). Alkoxycarbonyl groups include C_1-C_8, C_1-C_6 and C_1-C_4alkoxycarbonyl groups, which have from 1 to 8, 6 or 4 carbon atoms, respectively, in the alkyl portion of the group. "C_1alkoxycarbonyl" refers to $–C(=O)–O–CH_3$.

"Alkylamino" refers to a secondary or tertiary amine that has the general structure –NH–alkyl or –N(alkyl)(alkyl), wherein each alkyl is selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Such groups include, for example, mono- and di-(C_1-C_8alkyl)amino groups, in which each C_1-C_8alkyl may be the same or different, as well as mono- and di-(C_1-C_6alkyl)amino groups and mono- and di-(C_1-C_4alkyl)amino groups.

"Alkylaminoalkyl" refers to an alkylamino group linked via an alkylene group (*i.e.*, a group having the general structure –alkylene–NH–alkyl or –alkylene–N(alkyl)(alkyl)) in which each alkyl is

selected independently from alkyl, cycloalkyl and (cycloalkyl)alkyl groups. Alkylaminoalkyl groups include, for example, mono- and di-(C_1-C_8alkyl)aminoC_1-C_6alkyl, mono- and di-(C_1-C_6alkyl)aminoC_1-C_6alkyl and mono- and di-(C_1-C_6alkyl)aminoC_1-C_4alkyl. "Mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl" refers to a mono- or di-(C_1-C_6alkyl)amino group linked via a single covalent bond or a C_1-C_4alkylene group. The following are representative alkylaminoalkyl groups:



It will be apparent that the definition of "alkyl" as used in the terms "alkylamino" and "alkylaminoalkyl" differs from the definition of "alkyl" used for all other alkyl-containing groups, in the inclusion of cycloalkyl and (cycloalkyl)alkyl groups (*e.g.*, (C_3-C_7cycloalkyl)C_0-C_6alkyl).

The term "aminocarbonyl" refers to an amide group (*i.e.*, –C(=O)NH_2). "Mono- or di-(C_1-C_6alkyl)aminocarbonylC_0-C_4alkyl" refers to an aminocarbonyl group in which one or both hydrogens are replaced with an independently selected C_1-C_6alkyl group, and which is linked via a single covalent bond or a C_1-C_4alkylene group.

The term "aminosulfonyl" refers to a sulfonamide group (*i.e.*, –SO_2NH_2). "Mono- or di-(C_1-C_6alkyl)aminosulfonylC_0-C_4alkyl" refers to an aminosulfonyl group in which one or both hydrogens are replaced with an independently selected C_1-C_6alkyl group, and which is linked via a single covalent bond or a C_1-C_4alkylene group.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

A "haloalkyl" is an alkyl group that is substituted with 1 or more independently chosen halogens (*e.g.*, "C_1-C_8haloalkyl" groups have from 1 to 8 carbon atoms; "C_1-C_6haloalkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; mono-, di-, tri-, tetra- or penta-chloroethyl; and 1,2,2,2-tetrafluoro-1-trifluoromethyl-ethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl.

A dash ("–") that is not between two letters or numbers is used to indicate a point of attachment for a substituent. For example, –C(=O)NH_2 is attached through the carbon atom.

A "carbocycle" has from 1 to 3 fused, pendant or spiro rings, each of which has only carbon ring members and each of which may, but need not, be bridged by an alkylene moiety. Typically, a carbocycle that has a single ring contains from 3 to 8 ring members (*i.e.*, C_3-C_8carbocycles); rings having from 4 or 5 to 7 ring members (*i.e.*, C_4-C_7carbocycles or C_5-C_7carbocycles) are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Carbocycles may be optionally substituted with a variety of substituents, as indicated. Unless otherwise specified, a carbocycle may be a cycloalkyl group (*i.e.*, each ring is saturated or partially saturated as described above) or an aryl group (*i.e.*, at least one ring within the group is aromatic). Representative aromatic carbocycles are phenyl, naphthyl, tetrahydronaphthyl and

biphenyl. In certain embodiments preferred carbocycles have a single ring, such as phenyl and C_3-C_8cycloalkyl groups.

Certain carbocycles recited herein are (C_3-C_{10}carbocycle)C_0-C_4alkyl groups (*i.e.*, groups in which a 3- to 10-membered carbocyclic group (which may be cycloalkyl or aryl) is linked via a single covalent bond or C_1-C_4alkylene). Phenyl groups linked via a single covalent bond or C_1-C_6alkylene are designated phenylC_0-C_4alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl). A phenylC_0-C_4alkoxy group is a phenyl ring linked via an oxygen bridge or via an alkoxy group having from 1 to 4 carbon atoms (*e.g.*, phenoxy or benzoxy). When substituted, it will be apparent that such groups may be substituted on the ring portion and/or on the alkylene portion of the group.

A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom independently chosen from O, S and N, with the remaining ring atoms being carbon). Additional rings, if present, may be heterocyclic or carbocyclic. Typically, a heterocyclic ring comprises 1, 2, 3 or 4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 4 to 8 ring members (rings having from 4 or 5 to 7 ring members are recited in certain embodiments) and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain heterocycles comprise a sulfur atom as a ring member; in certain embodiments, the sulfur atom is oxidized to SO or SO_2. Heterocycles may be optionally substituted with a variety of substituents, as indicated. Certain heterocycles are 4- to 10-membered and comprise one or two rings; in certain embodiments, such heterocycles are monocyclic (*e.g.*, 4- to 8-membered, 5- to 7-membered, 4- to 7-membered, or 5- or 6-membered).

Certain heterocycles are heteroaryl groups (*i.e.*, at least one ring within the group is aromatic), such as a 5- to 10-membered heteroaryl (which may be monocyclic or bicyclic) or a 6-membered heteroaryl (*e.g.*, pyridyl or pyrimidyl). For heteroaryl groups containing multiple rings, it will be apparent that the aromatic ring and the heterocycle may, but need not, be the same; for example, the term "heteroaryl" encompasses groups that comprise a phenyl ring and a heterocycloalkyl ring, such as 2,3-dihydro-1,4-benzodioxinyl and 1,3-benzodioxol-5-yl. Other heterocycles are heterocycloalkyl groups (*i.e.*, do not comprise an aromatic ring). Certain heterocycles may be linked by a single covalent bond or via an alkylene group, as indicated, for example, by the terms "(4- to 8-membered heterocycloalkyl)C_0-C_4alkyl" and "(4- to 10-membered heterocycle)C_0-C_4alkyl."

A "substituent," as used herein, is a molecular moiety that is covalently bonded to an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (such as a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically stable compound (*i.e.*, a

compound that can be isolated, characterized, and tested for biological activity) results from the substitution.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, with one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substituents).

"B_1," as used herein, refers to the human B_1 bradykinin receptor reported by Menke et al. (1994) *J. Biol. Chem. 269*:21583-21586, as well as allelic variants thereof and homologues thereof found in other species (*e.g.*, GenBank Accession Number AAX14712 for Macaca fascicularis).

The term "B_1 agonist" refers to a compound that binds B_1 and induces signal transduction mediated by B_1. Such induction may be determined using the representative calcium mobilization assay provided in Example 7. B_1 agonists include, for example, bradykinin and kallidin (lysyl-bradykinin), as well as peptide portions or variants of bradykinin or kallidin that bind B_1 and retain activity. Representative B_1 agonists include, but are not limited to, desArg^{9}bradykinin and desArg^{10}kallidin.

A "B_1 antagonist" is a compound that detectably inhibits signal transduction mediated by B_1. Such inhibition may be determined using the representative calcium mobilization assay provided in Example 7. Preferred B_1 antagonists have an IC_{50} of 5 μM or less in this assay, more preferably 2 μM or less, and still more preferably 1 μM or less, 500 nM or less, 100 nM or less or 10 nM or less. In certain embodiments, the B_1 antagonist is specific for B_1 (*i.e.*, the IC_{50} value in a similar assay performed using the B_2 receptor is greater than 2 μM and/or the IC_{50} ratio (B_2/B_1) is at least 10, preferably 100, and more preferably at least 1000). B_1 antagonists preferably have minimal agonist activity (*i.e.*, induce an increase in the basal activity of B_1 that is less than 5% of the increase that would be induced by one EC_{50} of the peptide agonist desArg^{10}kallidin, and more preferably have no detectable agonist activity within the assay described in Example 7). B_1 antagonists for use as described herein are generally non-toxic. B_1 antagonists include neutral antagonists and inverse agonists.

A "neutral antagonist" of B_1 is a compound that inhibits the activity of B_1 agonist (*e.g.*, desArg^{10}kallidin) at B_1, but does not significantly change the basal activity of the receptor (*i.e.*, within a calcium mobilization assay as described in Example 7 performed in the absence of agonist, B_1 activity is reduced by no more than 10%, more preferably by no more than 5%, and even more preferably by no more than 2%; most preferably, there is no detectable reduction in activity). Neutral antagonists may, but need not, also inhibit the binding of agonist to B_1.

An "inverse agonist" of B_1 is a compound that reduces the activity of B_1 below its basal activity level in the absence of activating concentrations of agonist. Inverse agonists may also inhibit the activity of agonist at B_1, and/or may inhibit binding of B_1 agonist to B_1. The reduction in basal activity of B_1 produced by an inverse agonist may be determined from a calcium mobilization assay, such as the assay of Example 7.

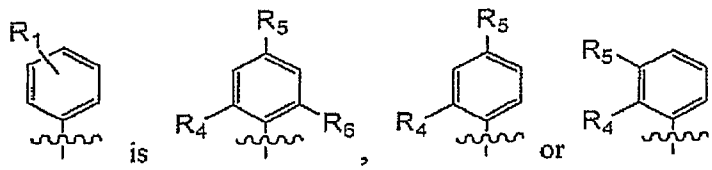
A "therapeutically effective amount" (or dose) is an amount that, upon administration to a patient, results in a discernible patient benefit (*e.g.*, provides detectable relief from a condition being treated). Such benefit may be detected using any appropriate criteria. A therapeutically effective amount or dose generally results in a concentration of compound in a body fluid (such as blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to result in detectable alteration in B_1-mediated signal transduction (using an assay provided herein). The discernible patient benefit may be apparent after administration of a single dose, or may become apparent following repeated administration of the therapeutically effective dose according to a predetermined regimen, depending upon the indication for which the compound is administered. For the treatment of pain, a discernible patient benefit is generally apparent after administration of a single therapeutically effective dose, although further benefit may become apparent following repeated administrations.

A "patient" is any individual treated with an aryl sulfonyl heterocycle as provided herein. Patients include humans, as well as other animals such as companion animals (*e.g.*, dogs and cats) and livestock. Patients may be experiencing one or more symptoms of a condition responsive to B_1 modulation or may be free of such symptom(s) (*i.e.*, treatment may be prophylactic in a patient considered to be at risk for the development of such symptoms).

B_1 MODULATORS

As noted above, the present invention provides aryl sulfonyl heterocycles of Formula I that may be used in a variety of contexts, including in the treatment of conditions responsive to B_1 modulation, as described herein. Such compounds may also be used within *in vitro* assays (*e.g.*, assays for B_1 activity), as probes for detection and localization of B_1 and within assays to identify other B_1 antagonists.

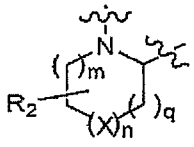
R_1, within Formula I and other formulas provided herein, generally represents optional substituents of the phenyl ring. Within certain compounds, the group designated:



is , or , in which R_4, R_5 and R_6 each represent one substituent independently chosen from R_1. Representative R_4, R_5 and R_6 groups include, for example, halogen, hydroxy, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy and C_1-C_6haloalkoxy. Within certain embodiments, R_5 is methyl or methoxy and R_4 and R_6 (if present) are each methyl; within other

embodiments, R_4 and R_6 (if present) each represent a halogen, and R_5 is a halogen, methoxy, trifluoromethyl or methyl.

Within certain embodiments of Formula I, and other formulas provided herein, n is 0, m is 1 and q is 0 or 1. In such embodiments, the group designated: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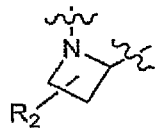
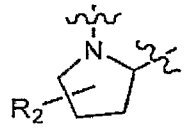

or

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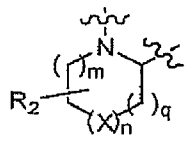
Within other embodiments, n is 1 and either (i) m is 1 and q is 1 or 2, or (ii) m is 2 and q is 1. In such embodiments, the group designated: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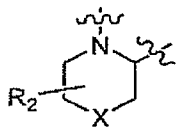
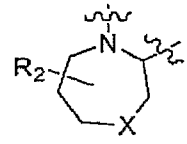
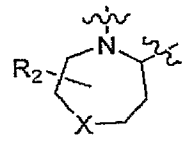
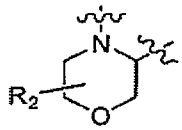

,

or

. Such groups include, for example,

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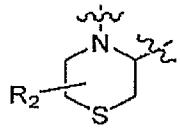
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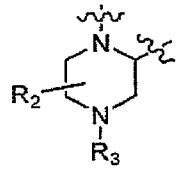
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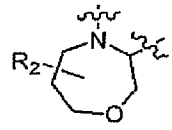
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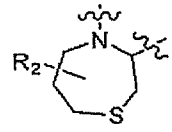
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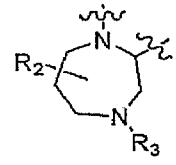
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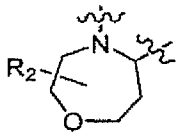
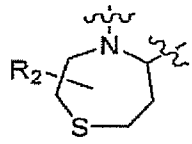
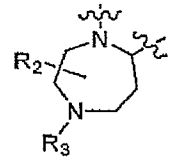
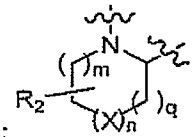
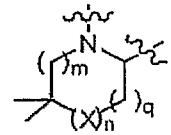
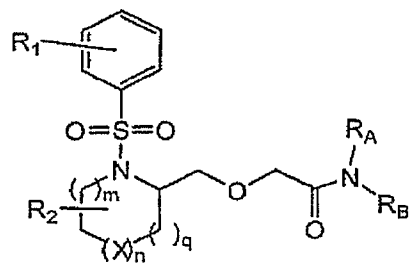
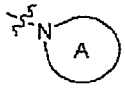
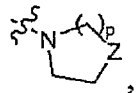

,

, and

.

R_2, within certain compounds of Formula I and other Formulas provided herein, represents from 0 to 4 substituents independently chosen from C_1-C_2alkyl. For example, in certain compounds, R_2 represents gem-dimethyl (*e.g.*, the group designated:

is

).

As noted above, the variable "Y" is -O-CH_2-, -N(R_{10})-CH_2-, -CH_2-CH_2-, -CH=CH-, -CH_2-O-CH_2-, -CH_2-CH_2-CH_2- or -O-CH_2-CH_2-. It will be apparent that the orientation of such groups within Formula I is retained; for example, when Y is -O-CH_2-, then the compound satisfies Formula III:


Formula III

Certain compounds of Formula I further satisfy Formula II, as described above. Within certain embodiments of Formula II, the group designated:

 is, for example,  , wherein

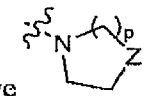
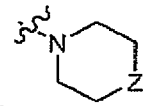
p is 0, I, 2 or 3;

Z is CR_7R_8 or NR_9;

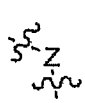
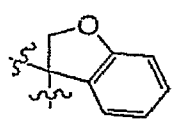
R_7 and R_8 are independently chosen from: (i) hydrogen, hydroxy and cyano; and (ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl and (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl; or

R_7 and R_8 are taken together to form a spiro 4- to 10-membered heterocycle that is substituted with from 0 to 2 substituents independently chosen from hydroxy, oxo, cyano and C_1-C_6alkyl; and

R_9 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl or (4- to 10-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl.

The group  may, optionally, be further substituted (*e.g.*, with C_1-C_6alkyl or oxo) at one or more ring carbon atoms. Representative  groups include, for example,  .

Within certain embodiments, Z is CR_7R_8, where R_7 and R_8 are as described above. Representative R_7 groups include, for example, hydrogen, hydroxy, cyano and C_1-C_6alkyl; representative R_8 groups include, for example, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, phenylC_0-C_4alkyl and (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_4alkyl and C_1-C_4alkoxy. Within certain such compounds, R_8 is mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl or (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl that is optionally substituted with C_1-C_2alkyl. Alternatively, R_7 and R_8 are taken together to form a spiro 4- to 10-membered heterocycle that is substituted with from 0 to 2 substituents independently chosen from hydroxy, oxo, cyano and C_1-C_6alkyl; for example,

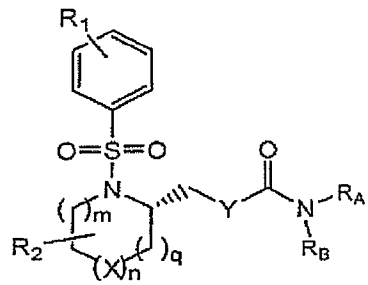
 is  , within certain such compounds.

With further embodiments, Z is NR_9, wherein R_9 is as described above. Representative R_9 groups include, for example, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from

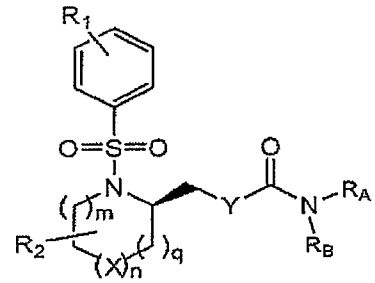
halogen, hydroxy, cyano, oxo and C_1-C_6alkyl. Within certain such compounds, R_9 is C_1-C_6alkyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl or (5- to 7-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl.

Within certain compounds of Formula I, R_A is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, or mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl; and R_B is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, or (5- or 6-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 6 substituents independently chosen from: (i) amino, halogen, hydroxy, cyano and oxo; and (ii) C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, phenylC_0-C_4alkyl and (5- or 6-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from amino, cyano, halogen, hydroxy, C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, mono- or di-(C_1-C_6alkyl)amino, phenylC_0-C_4alkyl and phenylC_0-C_4alkoxy. Representative R_A groups include, for example, C_1-C_6alkyl and C_2-C_6alkyl ether. Representative R_B groups include, for example, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, and (5- or 6-membered heterocycloalkyl)C_0-C_4alkyl, each of which is optionally substituted.

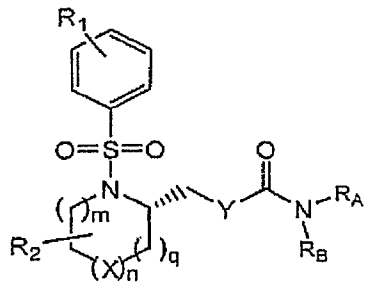
As noted above, Formulas provided herein encompass non-racemic compounds and racemic mixtures. For example, certain compounds of Formula I satisfy Formula Ia or Formula Ib, and certain compounds of Formula II satisfy Formula IIa or Formula IIb:



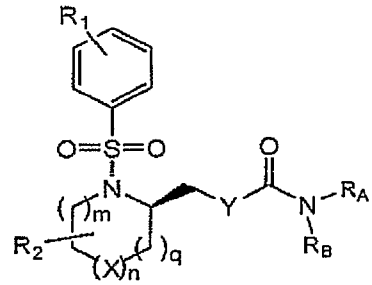
Formula Ia



Formula Ib

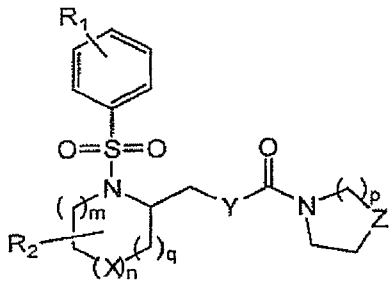


Formula IIa

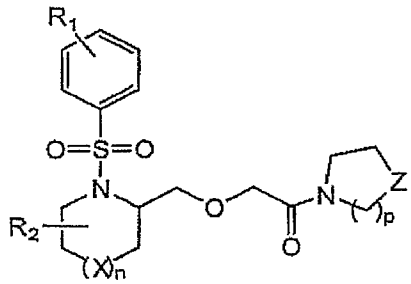


Formula IIb

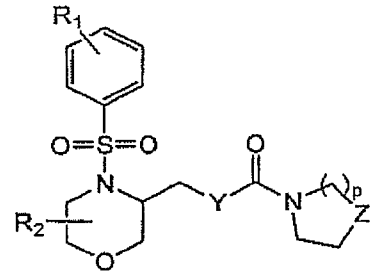
Certain compounds provided herein further satisfy one or more of the following Formulas, in which s is an integer ranging from 1 to 4, R_C and R_D are independently hydrogen or C_1-C_6alkyl, and the remaining variables are as described above:



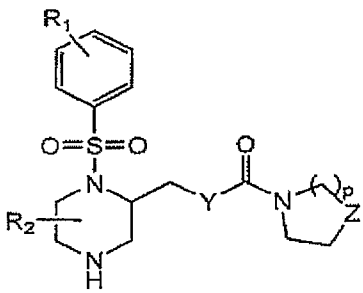
Formula IV



Formula V



Formula VI



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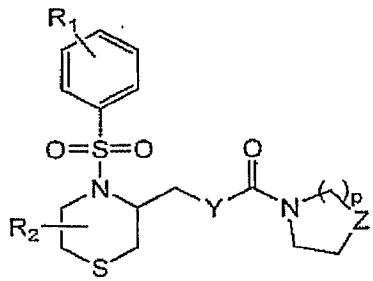

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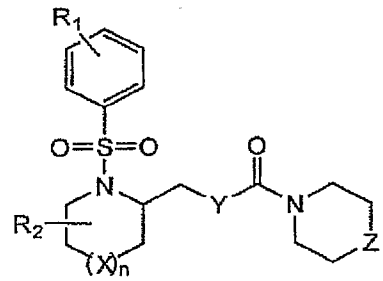

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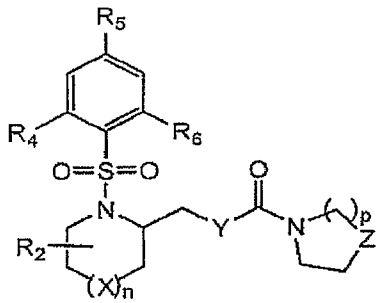
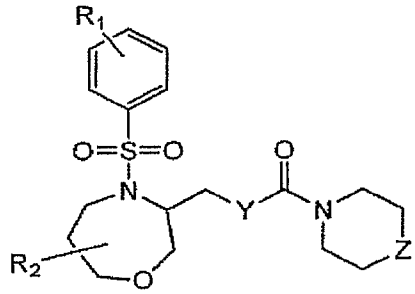
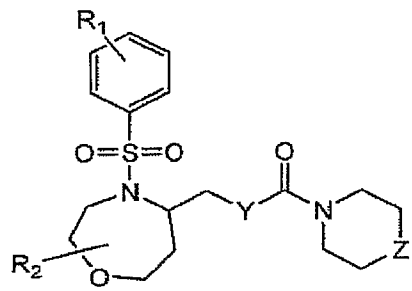


Formula X



Formula XI



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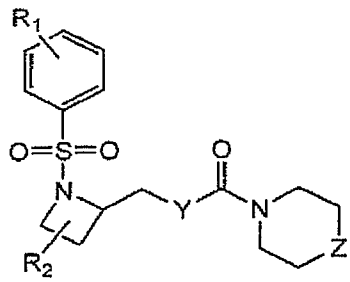
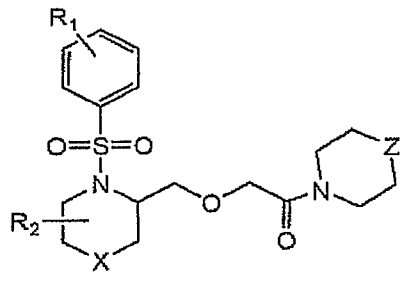
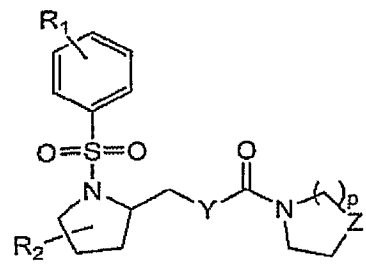


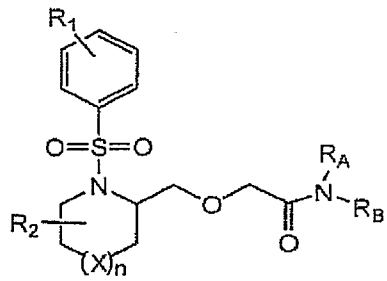
Formula XIII



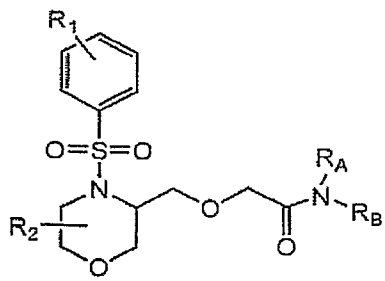
Formula XIV



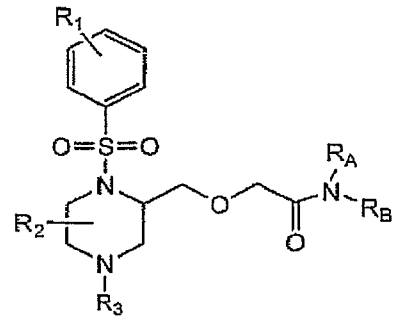
Formula XV



Formula XVI



Formula XVII



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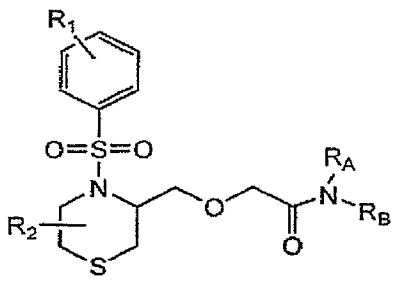
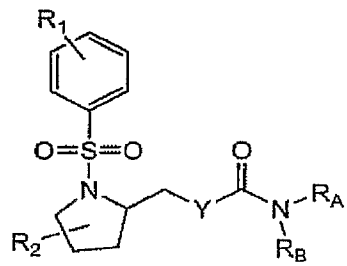
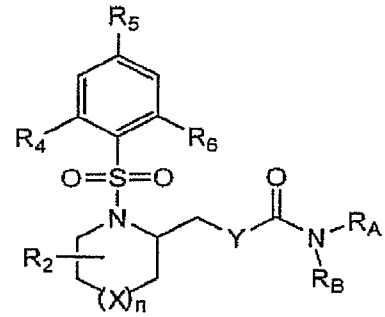


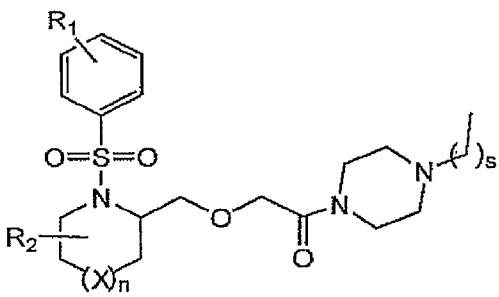
Formula XIX



Formula XX



Formula XXI



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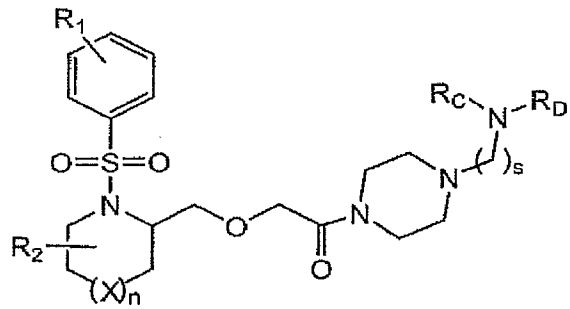
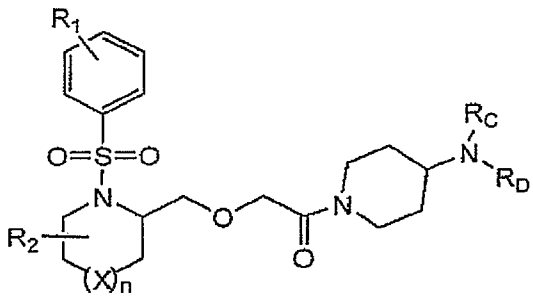


Formula XXIII



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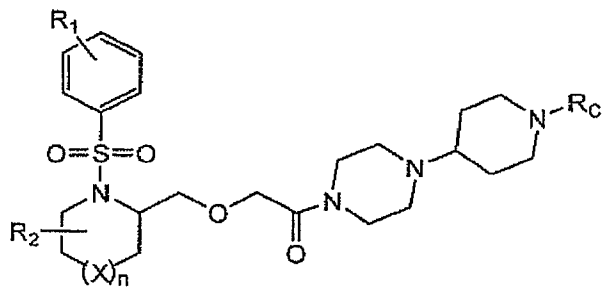
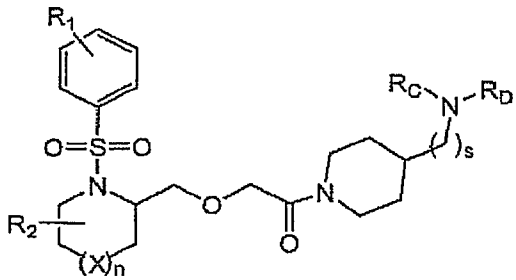


Formula XXV



Formula XXVI

Representative compounds provided herein include, but are not limited to, those specifically described in the Examples below. It will be apparent that the specific compounds recited herein are representative only, and are not intended to limit the scope of the present invention. Further, as noted above, all compounds of the present invention may be present as a free acid or base or as a pharmaceutically acceptable salt.

As noted above, within certain aspects, compounds provided herein are B_1 modulators. In addition, certain compounds provided herein display B_1 specificity. B_1 modulator activity may be confirmed using a calcium mobilization assay, such as the assay described in Example 7, herein.

If desired, binding activity of the compounds provided herein to B_1 may be confirmed using the representative assay described in Example 6, herein, or using an assay described by Fox et al. (2005) *Br. J. Pharmacol. 144*:889-99. Preferred B_1 modulators exhibit a K_i within such an assay of 5 micromolar or less, more preferably 2 micromolar or less, 1 micromolar or less, 500 nanomolar or less, 100 nanomolar or less or 10 nanomolar or less.

In vivo activity of B_1 modulators provided herein may be confirmed using any of a variety of animal models including, but not limited to, those described in the following documents (each of which is hereby incorporated by reference for its disclosure of the recited animal model):

Wood et al. (2003) *J. Med. Chem. 46*:1803-06 – carrageenan-induced mechanical pressure hyperalgesia;

Conley et al. (2005) *Eur. J. Pharmacol. 527*:44-51 – thermal antinociception and carrageenan-induced mechanical pressure hypersensitivity;

Gougat et al. (2004) *J. Pharmacol. Exper. Therap. 309*:661-669 – UV irradiation-induced thermal hyperalgesia and chronic constriction of the sciatic nerve-induced neuropathy and in ischemia-induced injury;

Fox et al. (2005) *Br. J. Pharmacol. 144*:889-99 – complete Freund's adjuvant-induced mechanical pressure hypersensitivity;

Gabra et al. (2005) *J. Neuropathol. Exp. Neurol.* 64:782-89 – diabetes-induced peripheral neuropathic pain;

Pesquero et al. (2000) *Proc. Natl. Acad. Sci. USA 97*:8140-45 – carrageenan-induced pleurisy (inflammation around the lung);

Lawson et al. (2005) *Eur. J. Pharmacol. 514*:69-78 – diabetes-induced vascular disease;

Hirata et a (2003) *Eur. J. Pharmacol. 474*:255-60 – ACE inhibitor-induced cough;

Mazzuferi et al. (2005) *Neuroscience. 135*:979-86 – neuronal hyperexcitability in epilepsy.

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally bioavailable to an extent allowing for therapeutically effective doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a

preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vivo* half-life allowing for Q.I.D. dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier may be desirable. Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described herein.

As noted above, preferred compounds provided herein are nontoxic. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). In addition, a highly preferred nontoxic compound generally satisfies one or more of the following criteria: (1) does not substantially inhibit cellular ATP production; (2) does not significantly prolong heart QT intervals; (3) does not cause substantial liver enlargement, or (4) does not cause substantial release of liver enzymes.

As used herein, a compound that does not substantially inhibit cellular ATP production is a compound that satisfies the criteria set forth in Example 8, herein. In other words, cells treated as described in Example 8 with 100 μM of such a compound exhibit ATP levels that are at least 50% of the ATP levels detected in untreated cells. In more highly preferred embodiments, such cells exhibit ATP levels that are at least 80% of the ATP levels detected in untreated cells.

A compound that does not significantly prolong heart QT intervals is a compound that does not result in a statistically significant prolongation of heart QT intervals (as determined by electrocardiography) in guinea pigs, minipigs or dogs upon administration of a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound. In certain preferred embodiments, a dose of 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally does not result in a statistically significant prolongation of heart QT intervals. By "statistically significant" is meant results varying from control at the $p<0.1$ level or more preferably at the $p<0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

A compound does not cause substantial liver enlargement if daily treatment of laboratory rodents (*e.g.*, mice or rats) for 5-10 days with a dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound results in an increase in liver to body weight ratio that is no more than 100% over matched controls. In more highly preferred embodiments, such doses do not cause liver enlargement of more than 75% or 50% over matched controls. If non-rodent mammals (*e.g.*, dogs) are used, such doses should not result in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls. Preferred doses within such assays include 0.01, 0.05. 0.1, 0.5, 1, 5, 10, 40 or 50 mg/kg administered parenterally or orally.

Similarly, a compound does not promote substantial release of liver enzymes if administration of twice the minimum dose that yields a serum concentration equal to the EC_{50} or IC_{50} for the compound does not elevate serum levels of ALT, LDH or AST in laboratory rodents by more than 100% over matched mock-treated controls. In more highly preferred embodiments, such doses do not elevate such serum levels by more than 75% or 50% over matched controls. Alternatively, a compound does not promote substantial release of liver enzymes if, in an *in vitro* hepatocyte assay, concentrations (in culture media or other such solutions that are contacted and incubated with hepatocytes *in vitro*) that are equal to the EC_{50} or IC_{50} for the compound do not cause detectable release of any of such liver enzymes into culture medium above baseline levels seen in media from matched mock-treated control cells. In more highly preferred embodiments, there is no detectable release of any of such liver enzymes into culture medium above baseline levels when such compound concentrations are five-fold, and preferably ten-fold the EC_{50} or IC_{50} for the compound.

In other embodiments, certain preferred compounds do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity or CYP3A4 activity at a concentration equal to the EC_{50} or IC_{50} for the compound.

Certain preferred compounds are not clastogenic (*e.g.*, as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay or the like) at a concentration equal the EC_{50} or IC_{50} for the compound. In other embodiments, certain preferred compounds do not induce sister chromatid exchange (*e.g.*, in Chinese hamster ovary cells) at such concentrations.

For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. For example, such compounds may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. In addition, substitution with heavy isotopes such as deuterium (*i.e.*, ^{2}H) can afford certain therapeutic

advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

PREPARATION OF B_1 MODULATORS

Compounds provided herein may generally be prepared using standard synthetic methods. In general, starting materials are commercially available from suppliers such as Sigma-Aldrich Corp. (St. Louis, MO), or may be synthesized from commercially available precursors using established protocols. By way of example, a synthetic route similar to that shown in any of the following Schemes may be used, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon appreciated by those skilled in the art. It will be apparent that the reagents and synthetic transformations in the following Schemes can be readily modified to produce additional compounds of Formula I. Each variable in the following Schemes refers to any group consistent with the description of the compounds provided herein.

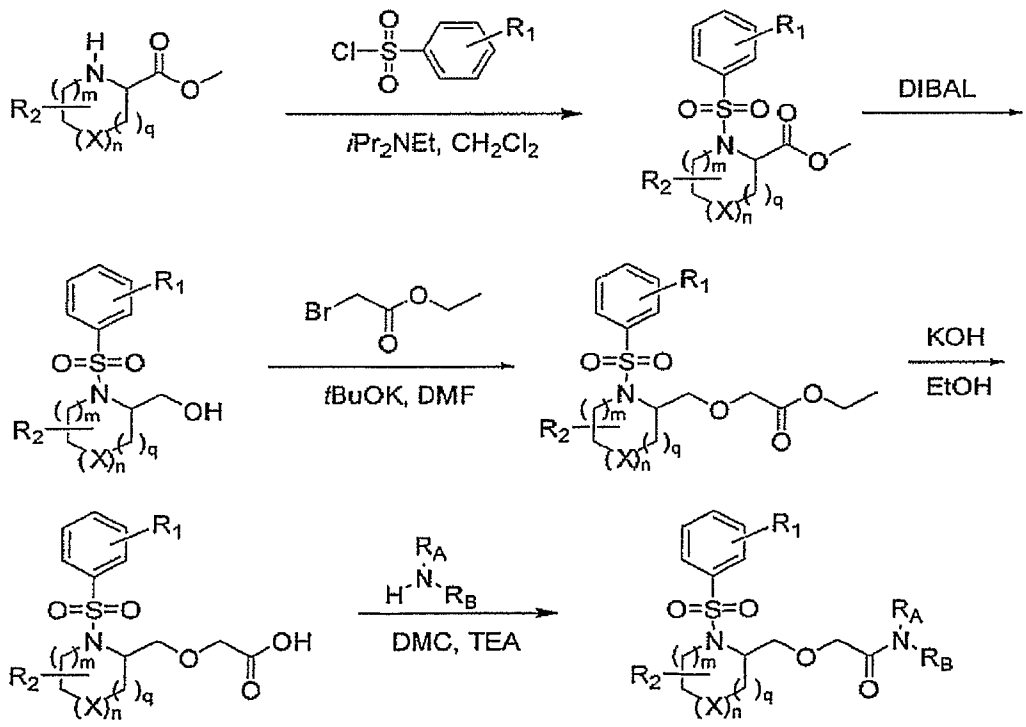
When a protecting group is required, an optional deprotection step may be employed. Suitable protecting groups and methodology for protection and deprotection, such as those described in *Protecting Groups in Organic Synthesis* by T. Greene, are well known. Compounds and intermediates requiring protection/deprotection will be readily apparent.

Certain abbreviations used in the following Schemes and in the Examples include:

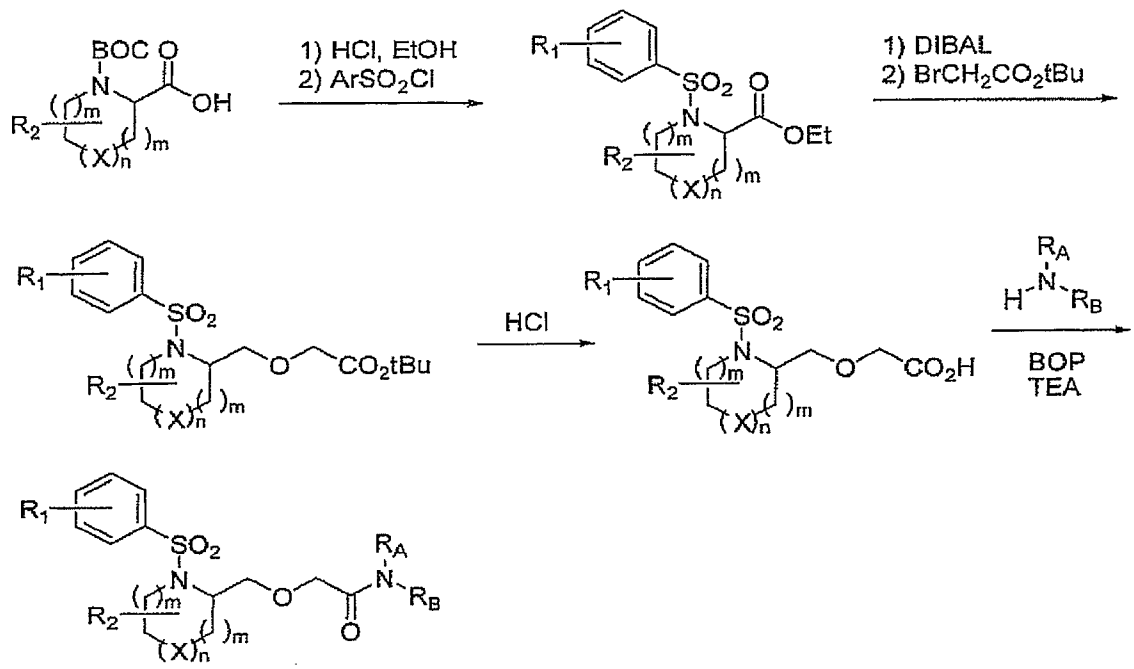
Ac_2O	acetic anhydride
AIBN	2,2'-Azobis(2-methylpropionitrile)
BOC	t-butoxycarbonyl
BOP	benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate
DIBAL	diisobutylaluminium hydride
DMA	*N,N*-dimethylacetamide
DMAP	*N,N*-dimethyl-4-aminopyridine
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
EtOH	ethanol
EtOAc	ethyl acetate
h	hour(s)
^{1}H NMR	proton nuclear magnetic resonance
iPr	isopropyl
LC-MS	liquid chromatography/mass spectrometry
Me	methyl
MHz	megahertz
M+1	mass + 1

min	minute(s)
MS	mass spectrometry
n-BuLi	n-butyl lithium
NMO	N-methylmorpholine N-oxide
δ	chemical shift
rt	room temperature
Ph	phenyl
SCX	strong cation exchange
SPE	solid phase extraction
tBu	*tert*-butyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TPAP	tetra-n-propylammonium perruthenate

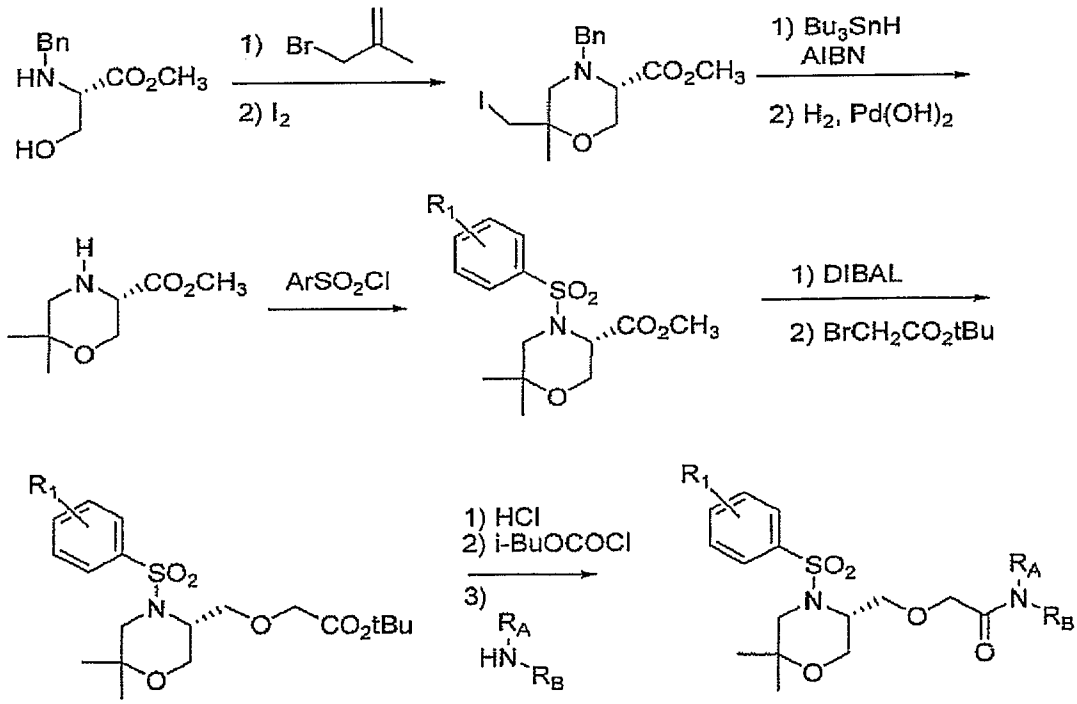
Scheme 1



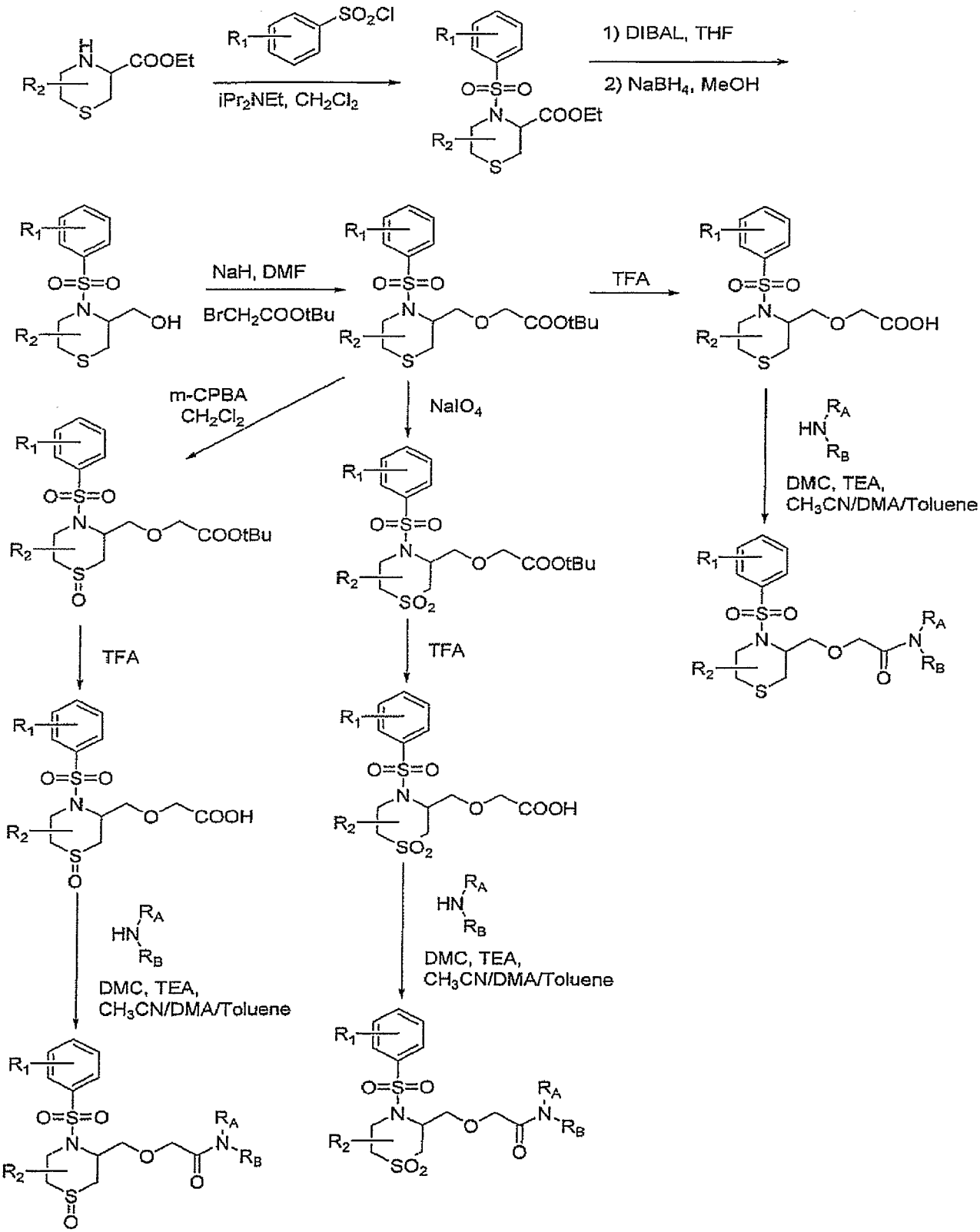
Scheme 2



Scheme 3



Scheme 4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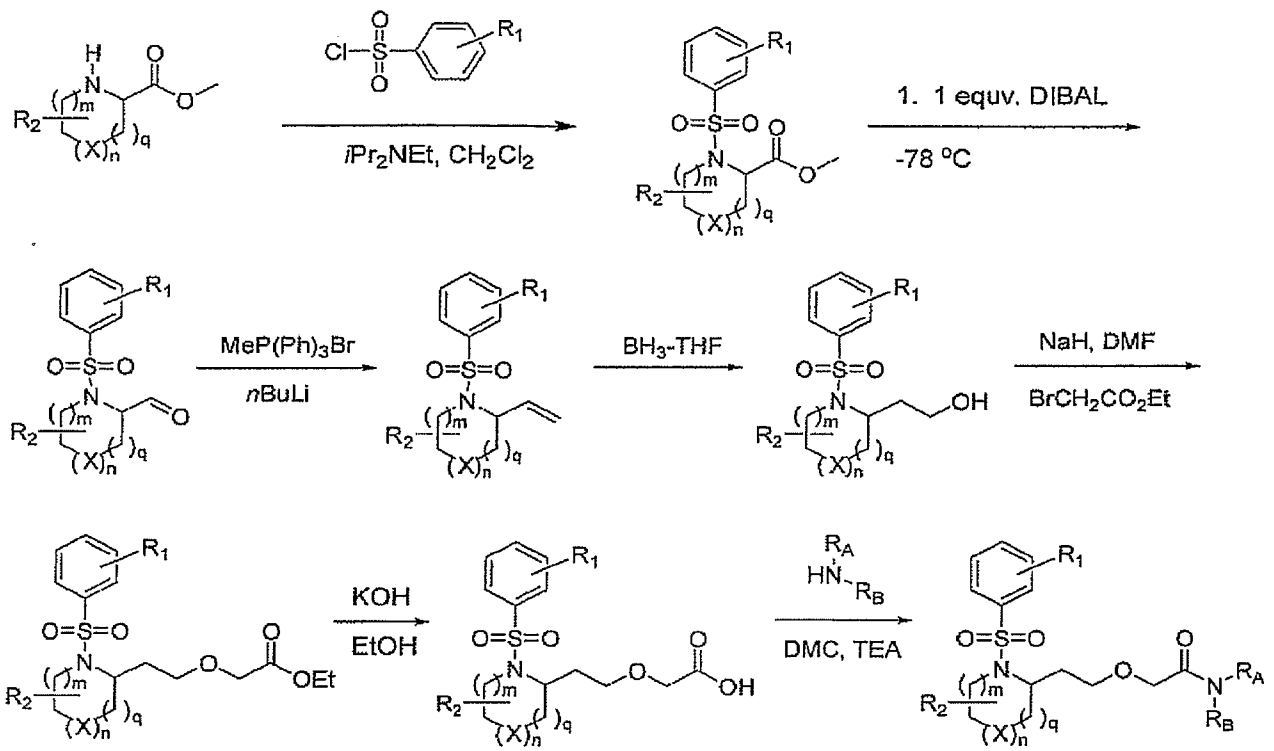
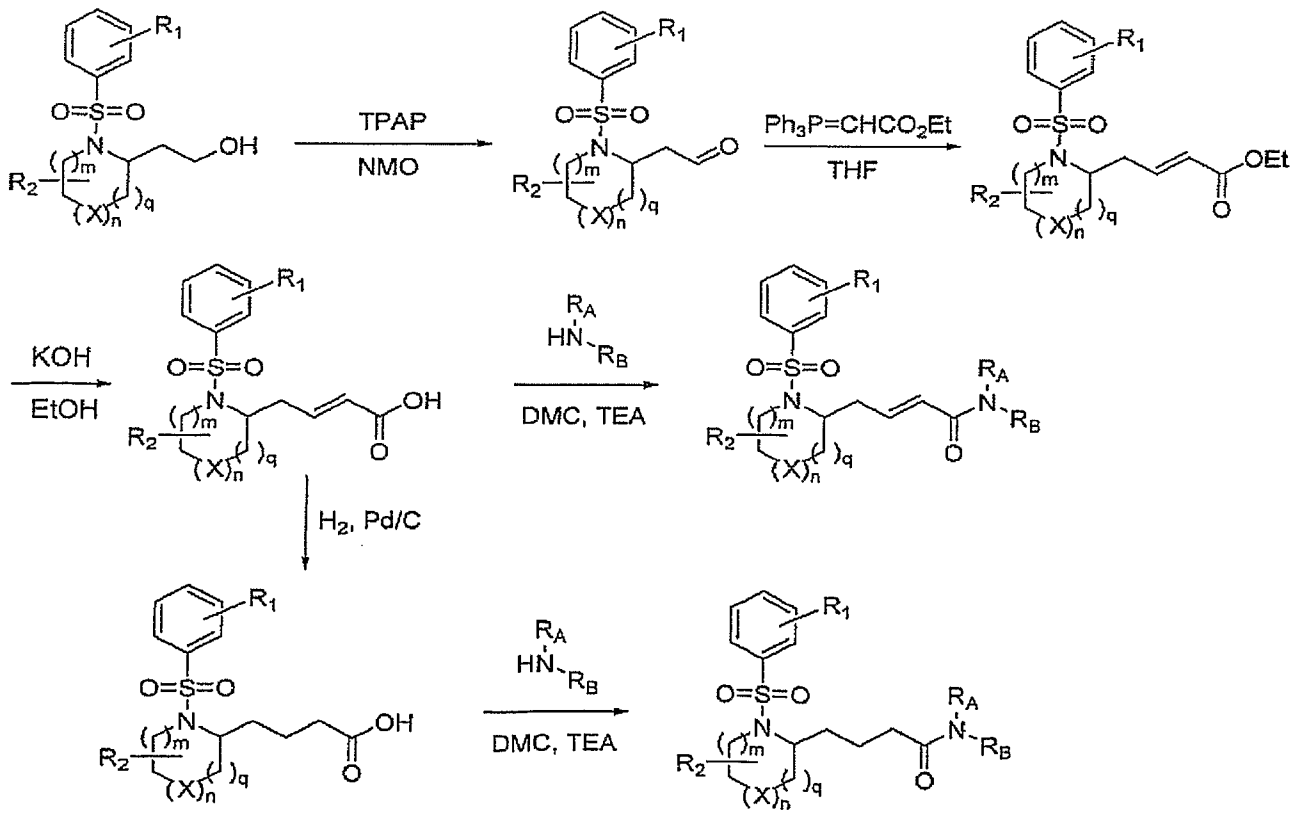
SO2Cl
iPr2NEt, CH2Cl2
1) DIBAL, THF
2) NaBH4, MeOH
OH
NaH, DMF
BrCH2COOtBu
COOtBu
COOH
TFA
m-CPBA
CH2Cl2
NaIO4
DMC, TEA,
CH3CN/DMA/Toluene

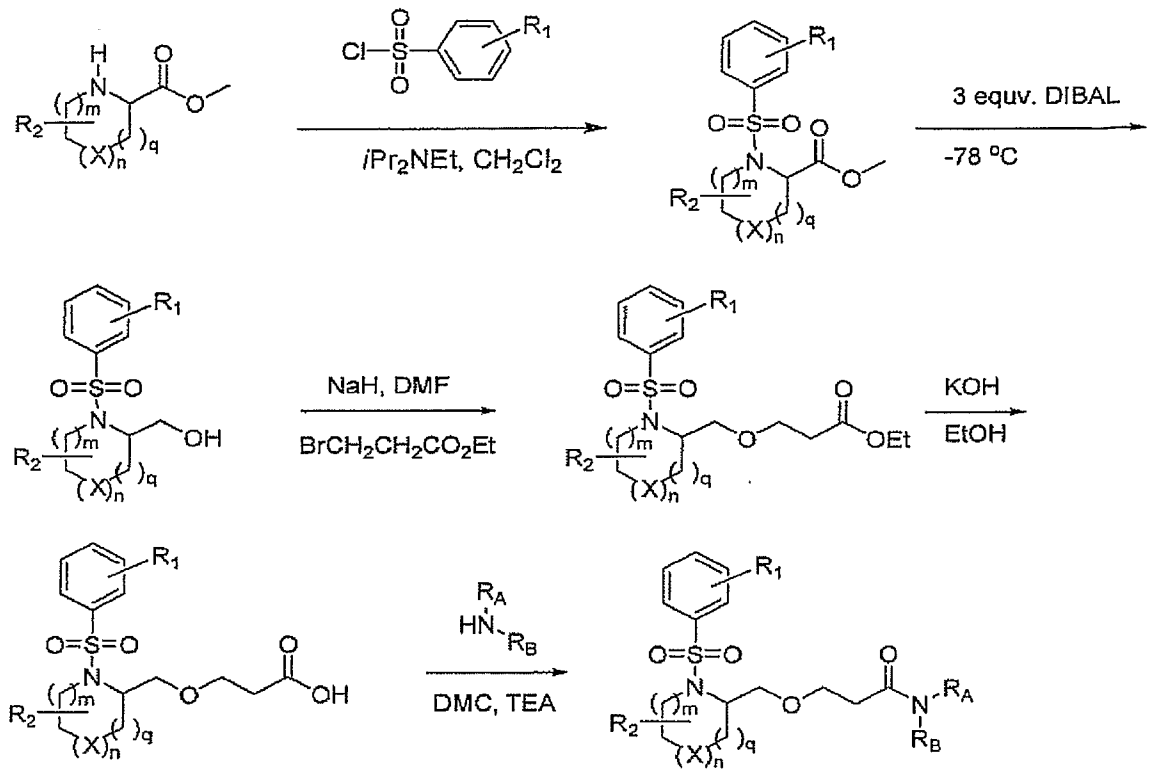
Scheme 5



Scheme 6



Scheme 7



In certain embodiments, a compound provided herein may contain one or more asymmetric carbon atoms, so that the compound can exist in different stereoisomeric forms. Such forms can be, for example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. Each radioisotope is preferably carbon (*e.g.*, ^{14}C), hydrogen (*e.g.*, ^{3}H), sulfur (*e.g.*, ^{35}S) or iodine (*e.g.*, ^{125}I). Tritium labeled compounds may also be prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate. Preparation of radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising one or more aryl sulfonyl heterocycles provided herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, sodium bicarbonate, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose, starch, mannitol or dextrans), proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives. In addition, other active ingredients may (but need not) be included in the pharmaceutical compositions provided herein.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions suitable for oral use are preferred. Such compositions include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, pharmaceutical compositions may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). Tablets may be formed using standard techniques, including dry granulation, direct compression and wet granulation. The tablets may be uncoated or they may be coated by known techniques.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions contain the active material(s) in admixture with suitable excipients, such as suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol,

condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also comprise one or more preservatives, such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and/or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient(s) in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be added to provide palatable oral preparations. Such suspensions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions may also be formulated as oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil), a mineral oil (*e.g.*, liquid paraffin) or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monoleate). An emulsion may also comprise one or more sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

Formulations for topical administration typically comprise a topical vehicle combined with active agent(s), with or without additional optional components. Suitable topical vehicles and additional components are well known in the art, and it will be apparent that the choice of a vehicle will depend on the particular physical form and mode of delivery. Topical vehicles include water; organic solvents such as alcohols (*e.g.*, ethanol or isopropyl alcohol) or glycerin; glycols (*e.g.*, butylene, isoprene or propylene glycol); aliphatic alcohols (*e.g.*, lanolin); mixtures of water and organic solvents and mixtures of organic solvents such as alcohol and glycerin; lipid-based materials such as fatty acids, acylglycerols (including oils, such as mineral oil, and fats of natural or synthetic origin), phosphoglycerides, sphingolipids and waxes; protein-based materials such as collagen and

gelatin; silicone-based materials (both non-volatile and volatile); and hydrocarbon-based materials such as microsponges and polymer matrices. A composition may further include one or more components adapted to improve the stability or effectiveness of the applied formulation, such as stabilizing agents, suspending agents, emulsifying agents, viscosity adjusters, gelling agents, preservatives, antioxidants, skin penetration enhancers, moisturizers and sustained release materials. Examples of such components are described in Martindale--The Extra Pharmacopoeia (Pharmaceutical Press, London 1993) and *Remington: The Science and Practice of Pharmacy,* 21st ed., Lippincott Williams & Wilkins, Philadelphia, PA (2005). Formulations may comprise microcapsules, such as hydroxymethylcellulose or gelatin-microcapsules, liposomes, albumin microspheres, microemulsions, nanoparticles or nanocapsules.

A topical formulation may be prepared in any of a variety of physical forms including, for example, solids, pastes, creams, foams, lotions, gels, powders, aqueous liquids and emulsions. The physical appearance and viscosity of such pharmaceutically acceptable forms can be governed by the presence and amount of emulsifier(s) and viscosity adjuster(s) present in the formulation. Solids are generally firm and non-pourable and commonly are formulated as bars or sticks, or in particulate form; solids can be opaque or transparent, and optionally can contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Creams and lotions are often similar to one another, differing mainly in their viscosity; both lotions and creams may be opaque, translucent or clear and often contain emulsifiers, solvents, and viscosity adjusting agents, as well as moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Gels can be prepared with a range of viscosities, from thick or high viscosity to thin or low viscosity. These formulations, like those of lotions and creams, may also contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product. Liquids are thinner than creams, lotions, or gels and often do not contain emulsifiers. Liquid topical products often contain solvents, emulsifiers, moisturizers, emollients, fragrances, dyes/colorants, preservatives and other active ingredients that increase or enhance the efficacy of the final product.

Suitable emulsifiers for use in topical formulations include, but are not limited to, ionic emulsifiers, cetearyl alcohol, non-ionic emulsifiers like polyoxyethylene oleyl ether, PEG-40 stearate, ceteareth-12, ceteareth-20, ceteareth-30, ceteareth alcohol, PEG-100 stearate and glyceryl stearate. Suitable viscosity adjusting agents include, but are not limited to, protective colloids or non-ionic gums such as hydroxyethylcellulose, xanthan gum, magnesium aluminum silicate, silica, microcrystalline wax, beeswax, paraffin, and cetyl palmitate. A gel composition may be formed by the addition of a gelling agent such as chitosan, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyquaterniums, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbomer or ammoniated glycyrrhizinate. Suitable surfactants include, but are not limited to,

nonionic, amphoteric, ionic and anionic surfactants. For example, one or more of dimethicone copolyol, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, lauramide DEA, cocamide DEA, and cocamide MEA, oleyl betaine, cocamidopropyl phosphatidyl PG-dimonium chloride, and ammonium laureth sulfate may be used within topical formulations. Suitable preservatives include, but are not limited to, antimicrobials such as methylparaben, propylparaben, sorbic acid, benzoic acid, and formaldehyde, as well as physical stabilizers and antioxidants such as vitamin E, sodium ascorbate/ascorbic acid and propyl gallate. Suitable moisturizers include, but are not limited to, lactic acid and other hydroxy acids and their salts, glycerin, propylene glycol, and butylene glycol. Suitable emollients include lanolin alcohol, lanolin, lanolin derivatives, cholesterol, petrolatum, isostearyl neopentanoate and mineral oils. Suitable fragrances and colors include, but are not limited to, FD&C Red No. 40 and FD&C Yellow No. 5. Other suitable additional ingredients that may be included a topical formulation include, but are not limited to, abrasives, absorbents, anti-caking agents, anti-foaming agents, anti-static agents, astringents (*e.g.*, witch hazel, alcohol and herbal extracts such as chamomile extract), binders/excipients, buffering agents, chelating agents, film forming agents, conditioning agents, propellants, opacifying agents, pH adjusters and protectants.

An example of a suitable topical vehicle for formulation of a gel is: hydroxypropylcellulose (2.1%); 70/30 isopropyl alcohol/water (90.9%); propylene glycol (5.1%); and Polysorbate 80 (1.9%). An example of a suitable topical vehicle for formulation as a foam is: cetyl alcohol (1.1%); stearyl alcohol (0.5%; Quaternium 52 (1.0%); propylene glycol (2.0%); Ethanol 95 PGF3 (61.05%); deionized water (30.05%); P75 hydrocarbon propellant (4.30%). All percents are by weight.

Typical modes of delivery for topical compositions include application using the fingers; application using a physical applicator such as a cloth, tissue, swab, stick or brush; spraying (including mist, aerosol or foam spraying); dropper application; sprinkling; soaking; and rinsing.

A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The compound(s) provided herein, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

Pharmaceutical compositions may also be formulated as suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore

melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Compositions for inhalation typically can be provided in the form of a solution, suspension or emulsion that can be administered as a dry powder or in the form of an aerosol using a conventional propellant (*e.g.*, dichlorodifluoromethane or trichlorofluoromethane).

Pharmaceutical compositions may be formulated for release at a pre-determined rate. Instantaneous release may be achieved, for example, via sublingual administration (*i.e.*, administration by mouth in such a way that the active ingredient(s) are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract). Controlled release formulations (*i.e.*, formulations such as a capsule, tablet or coated tablet that slows and/or delays release of active ingredient(s) following administration) may be administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at a target site. In general, a controlled release formulation comprises a matrix and/or coating that delays disintegration and absorption in the gastrointestinal tract (or implantation site) and thereby provides a delayed action or a sustained action over a longer period. One type of controlled-release formulation is a sustained-release formulation, in which at least one active ingredient is continuously released over a period of time at a constant rate. Preferably, the therapeutic agent is released at such a rate that blood (*e.g.*, plasma) concentrations are maintained within the therapeutic range, but below toxic levels, over a period of time that is at least 4 hours, preferably at least 8 hours, and more preferably at least 12 hours. Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends upon, for example, the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Controlled release may be achieved by combining the active ingredient(s) with a matrix material that itself alters release rate and/or through the use of a controlled-release coating. The release rate can be varied using methods well known in the art, including (a) varying the thickness or composition of coating, (b) altering the amount or manner of addition of plasticizer in a coating, (c) including additional ingredients, such as release-modifying agents, (d) altering the composition, particle size or particle shape of the matrix, and (e) providing one or more passageways through the coating. The amount of modulator contained within a sustained release formulation depends upon, for example, the method of administration (*e.g.*, the site of implantation), the rate and expected duration of release and the nature of the condition to be treated or prevented.

The matrix material, which itself may or may not serve a controlled-release function, is generally any material that supports the active ingredient(s). For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed. Active ingredient(s) may be

combined with matrix material prior to formation of the dosage form (*e.g.*, a tablet). Alternatively, or in addition, active ingredient(s) may be coated on the surface of a particle, granule, sphere, microsphere, bead or pellet that comprises the matrix material. Such coating may be achieved by conventional means, such as by dissolving the active ingredient(s) in water or other suitable solvent and spraying. Optionally, additional ingredients are added prior to coating (*e.g.*, to assist binding of the active ingredient(s) to the matrix material or to color the solution). The matrix may then be coated with a barrier agent prior to application of controlled-release coating. Multiple coated matrix units may, if desired, be encapsulated to generate the final dosage form.

In certain embodiments, a controlled release is achieved through the use of a controlled release coating (*i.e.*, a coating that permits release of active ingredient(s) at a controlled rate in aqueous medium). The controlled release coating should be a strong, continuous film that is smooth, capable of supporting pigments and other additives, non-toxic, inert and tack-free. Coatings that regulate release of the modulator include pH-independent coatings, pH-dependent coatings (which may be used to release modulator in the stomach) and enteric coatings (which allow the formulation to pass intact through the stomach and into the small intestine, where the coating dissolves and the contents are absorbed by the body). It will be apparent that multiple coatings may be employed (*e.g.*, to allow release of a portion of the dose in the stomach and a portion further along the gastrointestinal tract). For example, a portion of active ingredient(s) may be coated over an enteric coating, and thereby released in the stomach, while the remainder of active ingredient(s) in the matrix core is protected by the enteric coating and released further down the GI tract. pH dependent coatings include, for example, shellac, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, methacrylic acid ester copolymers and zein.

In certain embodiments, the coating is a hydrophobic material, preferably used in an amount effective to slow the hydration of the gelling agent following administration. Suitable hydrophobic materials include alkyl celluloses (*e.g.*, ethylcellulose or carboxymethylcellulose), cellulose ethers, cellulose esters, acrylic polymers (*e.g.*, poly(acrylic acid), poly(methacrylic acid), acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxy ethyl methacrylates, cyanoethyl methacrylate, methacrylic acid alkamide copolymer, poly(methyl methacrylate), polyacrylamide, ammonio methacrylate copolymers, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride) and glycidyl methacrylate copolymers) and mixtures of the foregoing. Representative aqueous dispersions of ethylcellulose include, for example, AQUACOAT® (FMC Corp., Philadelphia, PA) and SURELEASE® (Colorcon, Inc., West Point, PA), both of which can be applied to the substrate according to the manufacturer's instructions. Representative acrylic polymers include, for example, the various EUDRAGIT® (Rohm America, Piscataway, NJ) polymers, which may be used singly or in combination depending on the desired release profile, according to the manufacturer's instructions.

The physical properties of coatings that comprise an aqueous dispersion of a hydrophobic material may be improved by the addition or one or more plasticizers. Suitable plasticizers for alkyl celluloses include, for example, dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate and triacetin. Suitable plasticizers for acrylic polymers include, for example, citric acid esters such as triethyl citrate and tributyl citrate, dibutyl phthalate, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil and triacetin.

Controlled-release coatings are generally applied using conventional techniques, such as by spraying in the form of an aqueous dispersion. If desired, the coating may comprise pores or channels or to facilitate release of active ingredient. Pores and channels may be generated by well known methods, including the addition of organic or inorganic material that is dissolved, extracted or leached from the coating in the environment of use. Certain such pore-forming materials include hydrophilic polymers, such as hydroxyalkylcelluloses (*e.g.*, hydroxypropylmethylcellulose), cellulose ethers, synthetic water-soluble polymers (*e.g.*, polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone and polyethylene oxide), water-soluble polydextrose, saccharides and polysaccharides and alkali metal salts. Alternatively, or in addition, a controlled release coating may include one or more orifices, which may be formed my methods such as those described in US Patent Nos. 3,845,770; 4,034,758; 4,077,407; 4,088,864; 4,783,337 and 5,071,607. Controlled-release may also be achieved through the use of transdermal patches, using conventional technology (*see, e.g.,* US Patent No. 4,668,232).

Further examples of controlled release formulations, and components thereof, may be found, for example, in US Patent Nos. 4,572,833; 4,587,117; 4,606,909; 4,610,870; 4,684,516; 4,777,049; 4,994,276; 4,996,058; 5,128,143; 5,202,128; 5,376,384; 5,384,133; 5,445,829; 5,510,119; 5,618,560; 5,643,604; 5,891,474; 5,958,456; 6,039,980; 6,143,353; 6,126,969; 6,156,342; 6,197,347; 6,387,394; 6,399,096; 6,437,000; 6,447,796; 6,475,493; 6,491,950; 6,524,615; 6,838,094; 6,905,709; 6,923,984; 6,923,988; and 6,911,217; each of which is hereby incorporated by reference for its teaching of the preparation of controlled release dosage forms.

In addition to or together with the above modes of administration, a compound provided herein may be conveniently added to food or drinking water (*e.g.*, for administration to non-human animals including companion animals (such as dogs and cats) and livestock). Animal feed and drinking water compositions may be formulated so that the animal takes in an appropriate quantity of the composition along with its diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Aryl sulfonyl heterocycles(s) provided herein are generally administered in a therapeutically effective amount. Preferred systemic doses are no higher than 50 mg per kilogram of body weight per day (*e.g.*, ranging from about 0.001 mg to about 50 mg per kilogram of body weight per day), with oral doses generally being about 5-20 fold higher than intravenous doses (*e.g.*, ranging from 0.01 to 40 mg per kilogram of body weight per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage unit will vary depending, for example, upon the

patient being treated and the particular mode of administration. Dosage units will generally contain from about 10 μg to about 500 mg of an active ingredient. Optimal dosages may be established using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions provided herein may, but need not, further comprise one or more additional pharmaceutical agents, such as an anti-inflammatory agent or analgesic.

Anti-inflammatory agents include, for example, non-steroidal anti-inflammatory drugs (NSAIDs), non-specific and cyclooxygenase-2 (COX-2) specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, leflunomide, cyclosporine A, IM gold, minocycline, azathioprine, tumor necrosis factor (TNF) receptor antagonists, soluble TNF alpha receptor (etanercept), anti-TNF alpha antibodies (*e.g.*, infliximab and adalimumab), anti-C5 antibodies, interleukin-1 (IL-1) receptor antagonists (*e.g.*, anakinra or IL-1 trap), IL-18 binding protein, CTLA4-Ig (*e.g.*, abatacept), anti-human IL-6 receptor monoclonal antibody (*e.g.*, tocilizumab), LFA-3-Ig fusion proteins (*e.g.*, alefacept), LFA-1 antagonists, anti-VLA4 monoantibody (*e.g.*, natalizumab), anti-CD11a monoclonal antibody, anti-CD20 monoclonal antibody (*e.g.*, rituximab), anti-IL-12 monoclonal antibody, anti-IL-15 monoclonal antibody, CDP 484, CDP 870, chemokine receptor antagonists, selective iNOS inhibitors, p38 kinase inhibitors, integrin antagonists, angiogenesis inhibitors, and TMI-1 dual inhibitors. Further anti-inflammatory agents include meloxicam, rofecoxib, celecoxib, etoricoxib, parecoxib, valdecoxib and tilicoxib.

NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen or naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. One class of NSAIDs consists of compounds that inhibit cyclooxygenase (COX) enzymes; such compounds include celecoxib and rofecoxib. NSAIDs further include salicylates such as acetylsalicylic acid or aspirin, sodium salicylate, choline and magnesium salicylates, and salsalate, as well as corticosteroids such as cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, and prednisone.

Certain analgesics for use in combination with B_1 modulators provided herein are also anti-inflammatory agents, and are listed above. Other such medications are analgesic agents, including narcotic agents which typically act at one or more opioid receptor subtypes (*e.g.*, μ, κ and/or δ), preferably as agonists or partial agonists. Such agents include opiates, opiate derivatives and opioids, as well as pharmaceutically acceptable salts and hydrates thereof. Specific examples of narcotic analgesics include, within preferred embodiments, alfentanil, alphaprodine, anileridine, bezitramide, buprenorphine, butorphanol, codeine, diacetyldihydromorphine, diacetylmorphine, dihydrocodeine, diphenoxylate, ethylmorphine, fentanyl, heroin, hydrocodone, hydromorphone, isomethadone, levomethorphan, levorphane, levorphanol, meperidine, metazocine, methadone, methorphan, metopon, morphine, nalbuphine, opium extracts, opium fluid extracts, powdered opium, granulated

opium, raw opium, tincture of opium, oxycodone, oxymorphone, paregoric, pentazocine, pethidine, phenazocine, piminodine, propoxyphene, racemethorphan, racemorphan, sulfentanyl, thebaine and pharmaceutically acceptable salts and hydrates of the foregoing agents.

Other examples of narcotic analgesic agents include acetorphine, acetyldihydrocodeine, acetylmethadol, allylprodine, alphracetylmethadol, alphameprodine, alphamethadol, benzethidine, benzylmorphine, betacetylmethadol, betameprodine, betamethadol, betaprodine, clonitazene, codeine methylbromide, codeine-N-oxide, cyprenorphine, desomorphine, dextromoramide, diampromide, diethylthiambutene, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiamubutene, dioxaphetyl butyrate, dipipanone, drotebanol, ethanol, ethylmethylthiambutene, etonitazene, etorphine, etoxeridine, furethidine, hydromorphinol, hydroxypethidine, ketobemidone, levomoramide, levophenacylmorphan, methyldesorphine, methyldihydromorphine, morpheridine, morphine, methylpromide, morphine methylsulfonate, morphine-N-oxide, myrophin, naloxone, naltyhexone, nicocodeine, nicomorphine, noracymethadol, norlevorphanol, normethadone, normorphine, norpipanone, pentazocaine, phenadoxone, phenampromide, phenomorphan, phenoperidine, piritramide, pholcodine, proheptazoine, properidine, propiran, racemoramide, thebacon, trimeperidine and the pharmaceutically acceptable salts and hydrates thereof.

Further specific representative analgesic agents include, for example acetaminophen (paracetamol); aspirin and other NSAIDs described above; NR2B antagonists; capsaicin receptor antagonists; anti-migraine agents; anticonvulsants such as oxcarbazepine and carbamazepine; antidepressants (such as TCAs, SSRIs, SNRIs, substance P antagonists, etc.); spinal blocks; pentazocine/naloxone; meperidine; levorphanol; buprenorphine; hydromorphone; fentanyl; sufentanyl; oxycodone; oxycodone/acetaminophen, nalbuphine and oxymorphone. Still further analgesic agents include CB2-receptor agonists, such as AM1241, capsaicin receptor antagonists and compounds that bind to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, such as gabapentin and pregabalin.

Representative anti-migraine agents for use in combination with a B_1 modulator provided herein include CGRP antagonists, capsaicin receptor antagonists, ergotamines and 5-HT_1 agonists, such as sumatripan, naratriptan, zolmatriptan and rizatriptan.

Pharmaceutical compositions may be packaged for treating conditions responsive to B_1 modulation (*e.g.*, treatment of pain, inflammation or other disorder(s) recited herein). Packaged pharmaceutical preparations generally comprise a container holding a therapeutically effective amount of a pharmaceutical composition as described above and instructions (*e.g.*, labeling) indicating that the composition is to be used for treating a condition responsive to B_1 modulation in a patient (*e.g.*, pain or other disorder as indicated herein). In certain embodiments, a packaged pharmaceutical preparation comprises one or more aryl sulfonyl heterocycles provided herein and one or more additional agents in the same package, either in separate containers within the package or in the same container (*i.e.*, as a mixture). Preferred mixtures are formulated for oral administration (*e.g.*, as pills,

capsules, tablets or the like). In certain embodiments, the package comprises a label bearing indicia indicating that the components are to be taken together for the treatment of pain.

METHODS OF USE

Within certain aspects, the present invention provides methods for treating a condition responsive to B_1 modulation in a patient. The patient may be afflicted with such a condition, or may be free of symptoms but considered at risk for developing such a condition. A condition is "responsive to B_1 modulation" if the condition or symptom(s) thereof are alleviated, attenuated, delayed or otherwise improved by modulation of B_1 activity. In general, such methods comprise administering to the patient a therapeutically effective amount of at least one compound as provided herein.

Conditions responsive to B_1 modulation include, for example pain; inflammation including neuroinflammation (such as atherosclerosis), inflammation associated with airway diseases (*e.g.*, asthma, including allergic asthma, exercise-induced bronchoconstriction, occupational asthma, and other non-allergic asthmas), and inflammatory skin disorders (*e.g.*, psoriasis and eczema)); respiratory disorders including bronchoconstriction, asthma, chronic obstructive pulmonary disease (*e.g.*, emphysema), chronic cough (including ACE-inhibitor cough), adult respiratory distress syndrome, bronchitis, pneumonia, allergic rhinitis and vasomotor rhinitis; vascular edema (including diabetes-related vascular disease); and epilepsy.

Other conditions responsive to B_1 modulation include diabetes (*e.g.*, type II or non insulin dependent, as well as diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy, post capillary resistance and symptoms associated with insulitis), seizure disorders (*e.g.*, epilepsy), multiple sclerosis, liver disease, cardiovascular disorders (*e.g.*, atherosclerosis, congestive heart failure and myocardial infarction), neurodegenerative diseases (*e.g.*, Alzheimer's disease and Parkinson's disease) rheumatoid arthritis, infection, cancer, cranial trauma, rhinitis, septic shock, endotoxic and pancreatic shock, anaphylaxis, inflammatory bowel disease, irritable bowel syndrome, pancreatitis, cystitis, uveitis, vascular permeability, gingivitis, osteoporosis, benign prostatic hyperplasia, hyperactive bladder, cerebral edema, vasodilation, hypotension associated with sepsis, edema resulting from trauma associated with burns, sprains or fracture, cerebral edema, angiodema, Crohn's disease and ulcerative colitis. B_1 modulators may also be used as smooth muscle relaxants for treating spasms of the gastrointestinal tract of uterus. In certain embodiments, the condition responsive to B_1 modulation is pain or inflammation.

Pain that may be treated using the B_1 modulators provided herein includes, for example, acute, chronic, inflammatory, and neuropathic pain. Specific pain indications that may be treated as described herein include, but are not limited to, bone and joint pain (*e.g.*, pain associated with osteoarthritis or rheumatoid arthritis; various neuropathic pain syndromes (such as post-herpetic neuralgia, trigeminal neuralgia, reflex sympathetic dystrophy, diabetic neuropathy, Guillian Barre syndrome, fibromyalgia, oral neuropathic pain, phantom limb pain, post-mastectomy pain, peripheral

neuropathy, traumatic neuropathy, painful polyneuropathy, myofascial pain syndromes, MS-related neuropathy, HIV or AIDS-related neuropathy, and chemotherapy-induced and other iatrogenic neuropathies); visceral pain, (such as that associated with gastroesophageal reflux disease (GERD), irritable bowel syndrome, inflammatory bowel disease, pancreatitis, renal colic, interstitial cystitis, intestinal gas, gynecological disorders (*e.g.*, menstrual pain, dysmenorrhoea, pain associated with cystitis, labor pain, chronic pelvic pain, vulvodynia, chronic prostitis, and endometriosis), heart pain and abdominal pain, and urological disorders); dental pain (*e.g.*, toothache, denture pain, nerve root pain, pain resulting from periodontal disease, and pain due to dental surgery including operative and post-operative pain); stump pain; meralgia paresthetica; burning-mouth syndrome; pain associated with nerve and root damage, including as pain associated with peripheral nerve disorders (*e.g.*, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies including bilateral peripheral neuropathy, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis), causalgia, neuritis (including, for example, sciatic neuritis, peripheral neuritis, polyneuritis, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis and Gombault's neuritis), neuronitis, neuralgias (*e.g.*, those mentioned above, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial neuralgia, migranous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, mandibular joint neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia and vidian neuralgia); surgery-related pain; musculoskeletal pain; central nervous system pain (*e.g.*, pain due to brain stem damage, sciatica, and ankylosing spondylitis); and spinal pain, including spinal cord injury-related pain.

Headache, including headaches involving peripheral nerve activity may also be treated as described herein. Such headache pain includes, for example, sinus, cluster (*i.e.*, migranous neuralgia) and tension headaches, migraine, temporomandibular pain and maxillary sinus pain. For example, migraine headaches may be prevented by administration of a compound provided herein as soon as a pre-migrainous aura is experienced by the patient.

Further pain conditions that can be treated as described herein include Charcot's pains, ear pain, muscle pain, eye pain, orofacial pain (*e.g.*, odontalgia), repetitive motion pain, carpel tunnel syndrome, acute and chronic back pain (*e.g.*, lower back pain), gout, scar pain, hemorrhoidal pain, dyspeptic pains, angina, nerve root pain, "non-painful" neuropathies, complex regional pain syndrome, homotopic pain and heterotopic pain – including pain associated with carcinoma, often referred to as cancer-associated pain (*e.g.*, in patients with bone cancer), pain (and inflammation) associated with venom exposure (*e.g.*, due to snake bite, spider bite, or insect sting) and trauma-associated pain (*e.g.*, post-surgical pain, episiotomy pain, pain from cuts, musculoskeletal pain, bruises and broken bones, and burn pain, especially primary hyperalgesia associated therewith). Additional pain conditions that may be treated as described herein include pain associated with

autoimmune diseases or immunodeficiency disorders, hot flashes, burns, sunburn, and pain that results from exposure to heat, cold or external chemical stimuli.

In certain embodiments, pain treated with B_1 modulators provided herein is inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain or pain from osteoarthritis or trauma.

It will be apparent that compounds provided herein may be administered alone or in combination with one or more additional agents that are suitable for treating the disorder of interest. Within such combination therapy, the compound(s) and additional agent(s) may be present in the same pharmaceutical composition, or may be administered separately in either order. Representative anti-inflammatory agents and analgesics for use in combination therapy include those indicated above.

Within other aspects, B_1 modulators provided herein may be used within combination therapy for the treatment of conditions involving pain and/or inflammatory components. Such conditions include, for example, autoimmune disorders and pathologic autoimmune responses known to have an inflammatory component including, but not limited to, arthritis (especially rheumatoid arthritis), psoriasis, Crohn's disease, lupus erythematosus, irritable bowel syndrome, tissue graft rejection, and hyperacute rejection of transplanted organs. Other such conditions include trauma (*e.g.*, injury to the head or spinal cord), cardio- and cerebro-vascular disease and certain infectious diseases. Within such combination therapy, a B_1 modulator is administered to a patient along with an additional analgesic and/or anti-inflammatory agent. The B_1 modulator and additional analgesic and/or anti-inflammatory agent may be present in the same pharmaceutical composition, or may be administered separately in either order.

Administration to the patient can be by way of any means discussed above, including oral, topical, nasal or transdermal administration, or intravenous, intramuscular, subcutaneous, intrathecal, epidural, intracerebroventricular or like injection. Oral administration is preferred in certain embodiments (*e.g.*, formulated as pills, capsules, tablets or the like).

Treatment regimens may vary depending on the compound used and the particular condition to be treated. In general, a dosage regimen of 4 times daily or less is preferred, with 1 or 2 times daily particularly preferred. It will be understood, however, that the specific dose and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, the time of administration, the route of administration, the rate of excretion, any drug combination and the severity of the particular disease undergoing therapy. Dosages are generally as described above; in general, the use of the minimum dose sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented.

Suitable dosages for B_1 modulators (either alone or within such combination therapy) are generally as described above. Dosages and methods of administration of any additional agent(s) (e.g.,

anti-inflammatory and/or analgesic agents) can be found, for example, in the manufacturer's instructions or in the *Physician's Desk Reference.* In certain embodiments, combination administration results in a reduction of the dosage of the additional agent required to produce a therapeutic effect (*i.e.*, a decrease in the minimum therapeutically effective amount). Thus, preferably, the dosage of additional agent in a combination or combination treatment method of the invention is less than the maximum dose advised by the manufacturer for administration of the agent without combination with a compound of Formula I. More preferably this dose is less than ¾, even more preferably less than ½, and highly preferably less than ¼ of the maximum dose, while most preferably the dose is less than 10% of the maximum dose advised by the manufacturer for administration of the agent(s) when administered without combination administration as described herein. It will be apparent that the dose of compound as provided herein needed to achieve the desired effect may similarly be affected by the dose and potency of the additional agent.

Within separate aspects, the present invention provides a variety of non-pharmaceutical *in vitro* and *in vivo* uses for the compounds provided herein. For example, such compounds may be labeled and used as probes for the detection and localization of B_1 (in samples such as cell preparations or tissue sections, preparations or fractions thereof). In addition, compounds provided herein that comprise a suitable reactive group (such as an aryl carbonyl, nitro or azide group) may be used in photoaffinity labeling studies of receptor binding sites. In addition, compounds provided herein may be used as positive controls in assays for receptor activity, as standards for determining the ability of a candidate agent to bind to $_{B1}$, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such methods can be used to characterize B_1 receptors in living subjects. For example, a compound may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with a sample for a suitable incubation time (*e.g.*, determined by first assaying a time course of binding). Following incubation, unbound compound is removed (*e.g.*, by washing), and bound compound detected using any method suitable for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample containing labeled compound and a greater (*e.g.*, 10-fold greater) amount of unlabeled compound may be processed in the same manner. A greater amount of detectable label remaining in the test sample than in the control indicates the presence of B_1 in the sample. Detection assays, including receptor autoradiography (receptor mapping) of B_1 in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used

without further purification. Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein.

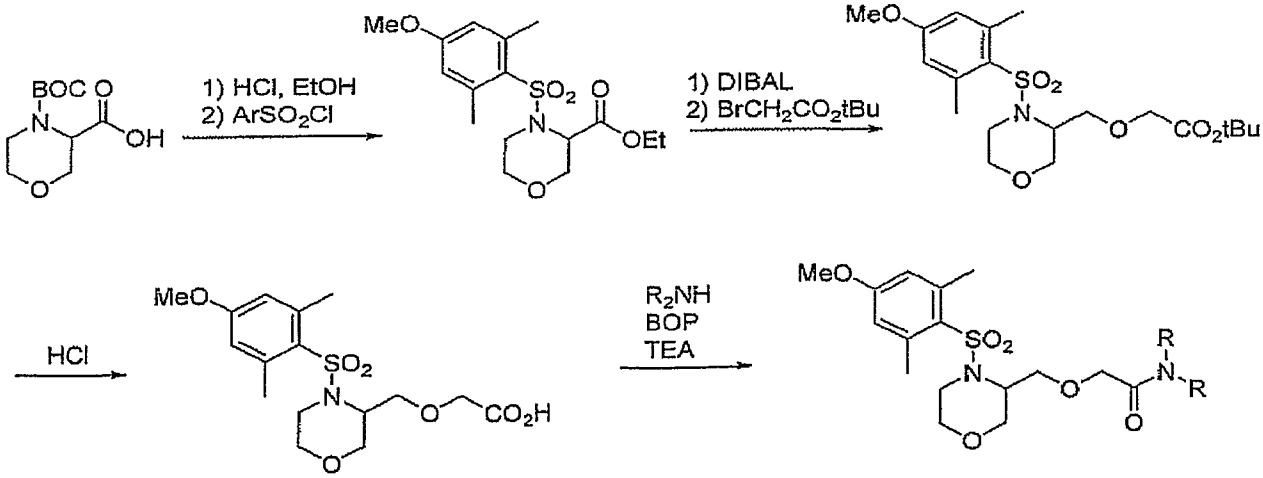
EXAMPLES

Mass spectroscopy data in the following Examples is Electrospray MS, obtained in positive ion mode using a Micromass Time-of-Flight LCT (Micromass, Beverly MA), equipped with a Waters 600 pump (Waters Corp.; Milford, MA), Waters 996 photodiode array detector, and a Gilson 215 autosampler (Gilson, Inc.; Middleton, WI). MassLynx (Advanced Chemistry Development, Inc; Toronto, Canada) version 4.0 software with OpenLynx Global Server™, OpenLynx™ and AutoLynx™ processing is used for data collection and analysis. MS conditions are as follows: capillary voltage = 3.5 kV; cone voltage = 30 V, desolvation and source temperature = 350°C and 120°C, respectively; mass range = 181-750 with a scan time of 0.22 seconds and an interscan delay of 0.05 min.

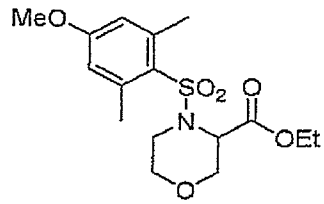
Sample volume of 1 microliter is injected onto a 50x4.6mm Chromolith SpeedROD RP-18e column (Merck KGaA, Darmstadt, Germany), and eluted using a 2-phase linear gradient at a flow rate of 6 ml/min. Sample is detected using total absorbance count over the 220-340nm UV range. The elution conditions are: Mobile Phase A - 95% water, 5% MeOH with 0.05% TFA; Mobile Phase B - 5% water, 95% MeOH with 0.025% TFA. The following gradient is used: 0-0.5 min 10-100%B, hold at 100%B to 1.2 min, return to 10%B at 1.21 min. Inject to inject cycle is 2.15 min.

EXAMPLE 1. SYNTHESIS OF REPRESENTATIVE ARYL SULFONYL HETEROCYCLES

A. 1-(4-(3-(DIMETHYLAMINO)PROPYL)PIPERAZIN-1-YL)-2-((4-(4-METHOXY-2,6-DIMETHYLPHENYLSULFONYL)MORPHOLIN-3-YL)METHOXY)ETHANONE

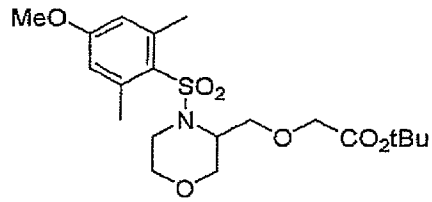


Step 1. Ethyl 4-(4-methoxy-2,6-dimethylphenylsulfonyl)-morpholinyl-3-carboxylate



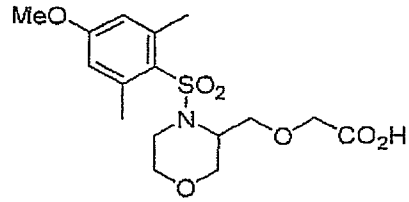
To a solution of N-BOC-morpholine-3-carboxylic acid (980 mg, 4.2mmol) is added 5 mL of a solution of 2M HCl in ether. The mixture is stirred at reflux for 15 hours, cooled to rt, and the solvent removed *in vacuo*. The resulting product is dissolved in 15 mL pyridine. 2,6-Dimethyl-4-methoxyphenylsulfonyl chloride (1.2 g, 5 mmol) and DMAP (15 mg) are added. The reaction mixture is stirred at 50 °C for 5 h, cooled to rt, diluted with 100 mL EtOAc, and transferred to a separatory funnel. The reaction mixture is washed three times with 50 mL water and once with 50 mL brine. The organic phase is dried over $MgSO_4$, filtered, and then concentrated *in vacuo*. The product is purified by flash chromatography eluting with 8/2 hexanes/EtOAc, followed by 1/1 hexanes/EtOAc to afford the title compound.

Step 2. *tert*-Butyl 2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)morpholin-3-yl)methoxy)acetate



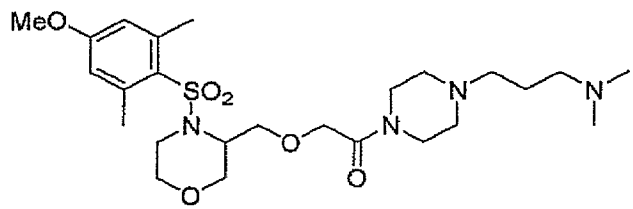
Ethyl 4-(4-methoxy-2,6-dimethylphenylsulfonyl)-morpholinyl-3-carboxylate (476 mg, 1.33 mmol) is dissolved in 10 mL dry THF. A solution of DIBAL (4 mL of a 1 M THF solution) is added and the reaction mixture is stirred at rt for 1 hr. Another 4 mL of DIBAL solution is then added and stirring is continued for another hour. The reaction is quenched by careful addition of solid $Na_2SO_4 \cdot 10H_2O$. The reaction mixture is filtered through Celite then concentrated *in vacuo*. The DIBAL reduction product is dissolved in 5 mL dry DMA at room temperature. Sodium hydride is added (63 mg of a 60% oil dispersion) followed by *tert*-butyl bromoacetate (0.22 mL, 1.5 mmol). The reaction mixture is stirred at room temperature for 15 h. The reaction mixture is diluted with 20 mL EtOAc, and then washed successively with saturated NH_4Cl, 1N NaOH, H_2O, and brine. The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product is purified by column chromatography eluting with 8/2 hexanes/EtOAc, followed by 6/4 hexanes/EtOAc to afford the title compound.

Step 3. 2-((4-(4-Methoxy-2,6-dimethylphenylsulfonyl)morpholin-3-yl)methoxy)acetic acid



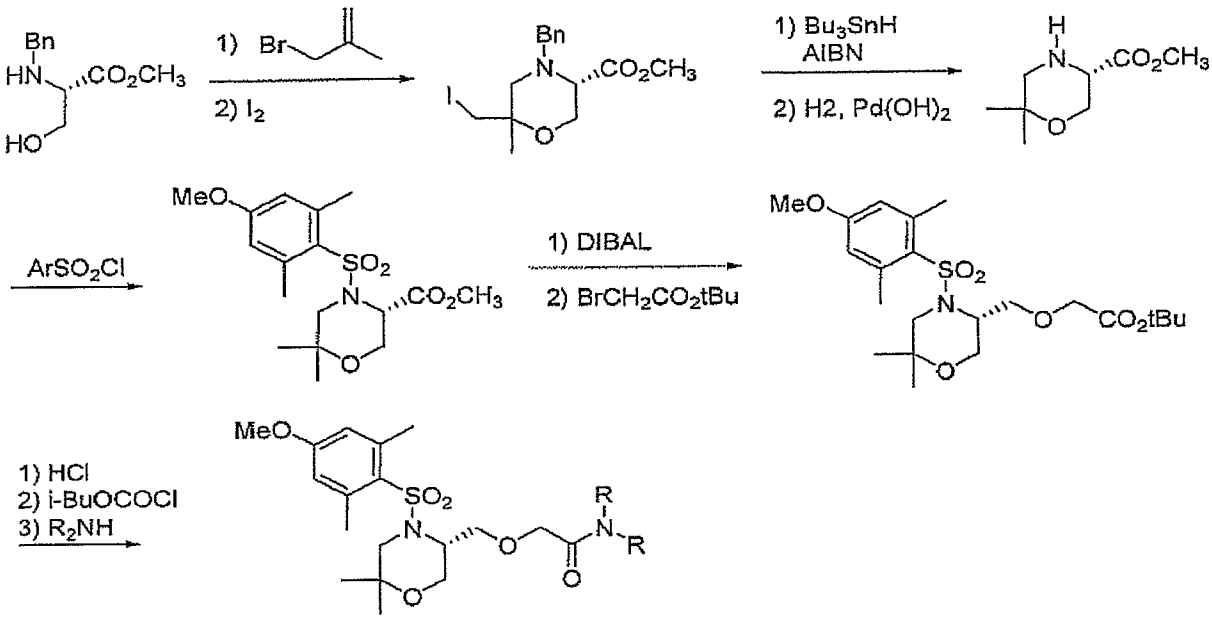
tert-Butyl 2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)morpholin-3-yl)methoxy)acetate (454 mg, 1.06 mmol) is dissolved in 5 mL dioxane. HCl (1.2 mL of a 2M HCl in dioxane solution) is added and the reaction mixture is stirred 15 h at 60 °C. The reaction mixture is cooled to rt and concentrated *in vacuo*. The product is purified by flash chromatography eluting with 6/4 hexanes/EtOAc followed by EtOAc to afford the title compound.

Step 4. 1-(4-(3-(Dimethylamino)propyl)piperazin-1-yl)-2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)morpholin-3-yl)methoxy)ethanone

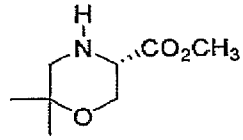


To a solution of 2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)morpholin-3-yl)methoxy)acetic acid (0.3 mL of a 0.2M solution of acid in DMA) is added 4-(3-(dimethylamino)propyl)piperazine (0.3 mL of a 0.2M solution in toluene) followed by BOP (100 mg, 0.23mmol) followed by TEA (0.1mL). The reaction mixture is stirred at 60 °C for 4 hours. The reaction mixture is cooled to room temperature, diluted with 1 mL EtOAc, and washed with 2 mL H_2O. The organic phase is applied to a 1g SCX cartridge and eluted with 5 mL MeOH to remove non-basic by-products followed by 5 mL 2N NH_3 in MeOH to elute the title compound. Removal of solvent affords the title compound as a white foam. ^{1}H NMR (400 MHz, CDCl3) δ: 6.63 (s, 2H), 4.11 (s, 2H), 4.05 (d, 1H), 3.94 (t, 1H), 3.81 (s, 3H), 3.77 (m, 2H), 3.73 (m, 2H), 3.57-3.60 (m, 4H), 3.40-3.42 (m, 4H), 3.22 (dt, 1H), 3.12 (dd, 1H), 2.60 (s, 6H), 2.34-2.44 (m, 6H), 2.29 (t, 2H), 2.21 (s, 6H), 1.65 (m, 2H). LC-MS *m/z* (M+H): 527.29.

B. (R)-2-((4-(4-METHOXY-2,6-DIMETHYLPHENYLSULFONYL)-6,6-DIMETHYLMORPHOLIN-3-YL)METHOXY)-1-(4-(1-METHYLPIPERIDIN-4-YL)PIPERAZIN-1-YL)ETHANONE



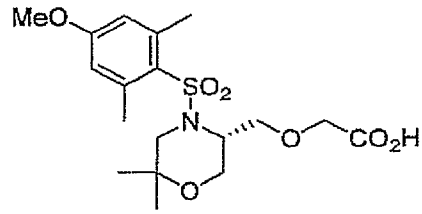
Step 1. (S)-Methyl 6,6-dimethylmorpholine-3-carboxylate



(S)-Methyl 2-(benzylamino)-3-hydroxypropanoate (27.4 g, 131 mmol) is combined with 3-bromo-2-methylpropene (25 mL, 248 mmol), K_2CO_3 (45 g, 327 mmol), and KI (4.3 g, 26 mmol) in 300 mL acetonitrile. The reaction mixture is stirred at rt for 3 days. Iodine (66 g, 262 mmol) is added and the reaction mixture is stirred an additional 2 h at rt. The reaction mixture is diluted with 300 mL ether and transferred to a separatory funnel. The solution is washed twice successively with 200 mL 1N Na_2SO_3, once with 200 mL saturated $NaHCO_3$, and once with 200 mL brine. The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product is purified by flash chromatography, eluting with 9/1 hexanes/EtOAc to afford (3S)-methyl 4-benzyl-6-(iodomethyl)-6-methylmorpholine-3-carboxylate as a 5/1 mixture of diastereomers. This mixture of diastereomers is combined with tributyltin hydride (73 mL, 272 mmol) in 400 mL refluxing toluene. AIBN (1 g, 6 mmol) dissolved in 40 mL toluene is added dropwise. After 2 h reflux, the reaction mixture is cooled to rt. Saturated aqueous KF solution (800 mL) is added and the resulting heterogeneous mixture is filtered through Celite and the solid washed with EtOAc. The combined solutions are transferred to a separatory funnel and washed twice with 200 mL saturated KF, and then once with 20 mL brine. The organic phase is dried over MgSO4, filtered and concentrated *in vacuo*. The product is purified by flash chromatography eluting with 95/5 hexanes/EtOAc followed by EtOAc to afford (S)-methyl 4-benzyl-6,6-dimethylmorpholine-3-carboxylate as a clear oil. This oil is dissolved in a mixture of 200 mL MeOH and 20 mL acetic acid. Palladium hydroxide (5 g, 20 wt. % on carbon) is added and the

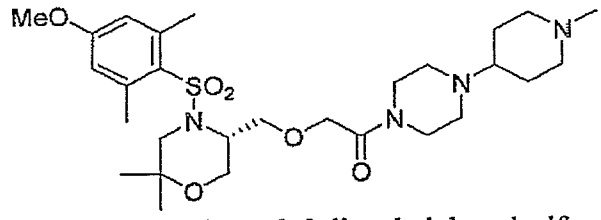
reaction mixture hydrogenated on a Paar apparatus at 50 psi for 10 h. An additional 5 g of palladium hydroxide is added and the hydrogenation is continued at 50 psi for another 25 h. The reaction mixture is filtered through Celite and concentrated *in vacuo* to afford the title product. 1H NMR (400 MHz, d-6-DMSO) d: 3.71-3.74 (m, 1H), 3.61-3.65 (m, 1H), 3.61 (s, 3H), 3.36 (m, 1H), 2.65 (d, 1H), 2.46 (d, 1H), 1.11 (s, 3H), 1.09 (s, 3H).

Step 2. (R)-2-((4-(4-Methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)acetic acid



(S)-Methyl 6,6-dimethylmorpholine-3-carboxylate (2.3 g, 13 mmol) is dissolved in 50 mL pyridine. 2,6-Dimethyl-4-methoxyphenylsulfonyl chloride (3.1 g, 13 mmol) and DMAP (15 mg) are added. The reaction mixture is stirred at 50 °C for 5 h. The reaction mixture is cooled to rt, diluted with 100 mL EtOAc, and transferred to a separatory funnel. The reaction mixture is washed three times with 50 mL water and once with 50 mL brine. The organic phase is dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The product is purified by flash chromatography eluting with 8/2 hexanes/EtOAc followed by 1/1 hexanes/EtOAc to afford (S)-methyl 4-(4-methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholine-3-carboxylate. This compound is dissolved in 8 mL of dry THF at 0 °C. DIBAL (8 mL of a 1M solution in THF) is added and the reaction mixture stirred 30 min at 0 °C. An additional 1 mL DIBAL solution is added and stirring is continued for 30 min. The reaction mixture is quenched by addition of solid $Na_2SO_4 \cdot 10H_2O$. The reaction mixture is filtered through Celite and concentrated *in vacuo* to afford (R)-(4-(4-methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methanol. This compound, without further purification, is dissolved in 10 mL DMA at rt. Potassium iodide (20 mg) and sodium hydride (140 mg of a 60% oil dispersion) are added, followed by bromo *tert*-butyl acetate (0.48 mL, 3.2 mmol). The reaction mixture is stirred for 2 days, and then diluted with 50 mL EtOAc, transferred to a separatory funnel, and washed once with 20 mL water and once with 20 mL brine. The organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product is purified by flash chromatography eluting with 9/1 hexanes/EtOAc to afford (R)-*tert*-butyl 2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)acetate. This compound is dissolved in 3 mL of 4 M HCl in dioxane, and stirred at 50 °C for 3 h. The reaction mixture is cooled to rt and concentrated *in vacuo*. The product is purified by flash chromatography, eluting with 1/1 hexanes/EtOAc to afford the title compound. LC-MS *m/z* (M+Na): 424.73.

Step 3. (R)-2-((4-(4-Methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)-1-(4-(1-methylpiperidin-4-yl)piperazin-1-yl)ethanone

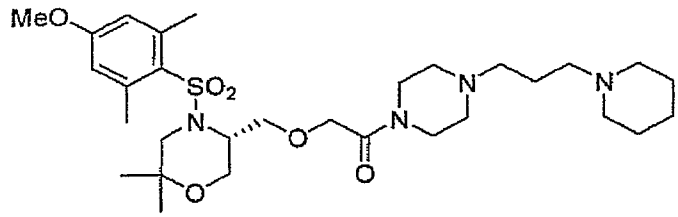


To a solution of (R)-2-((4-(4-methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)acetic acid (1 mL of a 0.2 M solution in 95/5 EtOAc/TEA) is added isobutylchloroformate (1 mL of a 0.2 M solution in toluene). The reaction mixture is stirred at rt for 5 min. 1-(1-Methylpiperidin-4-yl)piperazine (1.2mL of a 0.2M solution in toluene) is added and the reaction mixture is stirred 90 min at rt. The reaction mixture is diluted with 5 mL EtOAc and washed with 1 mL 1N NaOH. The organic phase is applied to a 10 g silica SPE cartridge and eluted with 10 mL EtOAc to remove non-polar impurities, followed by 10 mL 10/1/1 EtOAc/MeOH/TEA to elute the title compound. The solvent is removed *in vacuo* to afford the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.04 (s, 2H), 3.93 (dd, 1H), 3.84-3.86 (m, 1H), 3.81 (s, 3H), 3.76 (d, 1H), 3.70 (m, 1H), 3.56 (m, 3H), 3.47 (m, 1H), 3.39 (m, 2H), 2.99 (dd, 2H), 2.90 (d, 2H), 2.60 (s, 6H), 2.52 (m, 4H), 2.25 (s, 3H), 1.95 (t, 2H), 1.75 (d, 2H), 1.56 (m, 2H), 1.15 (s, 3H), 1.11 (s, 3H). LC-MS *m/z* (M+H): 567.17.

C. ADDITIONAL ARYL SULFONYL HETEROCYCLES

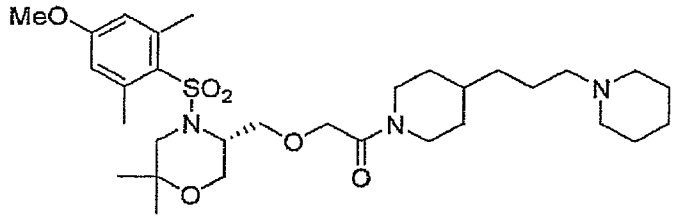
Using routine modifications, the starting materials may be varied and additional steps employed to produce other aryl sulfonyl heterocycles, including the following:

1. (R)-2-((4-(4-Methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)-1-(4-(3-(piperidin-1-yl)propyl)piperazin-1-yl)ethanone



^{1}H NMR (400 MHz, CDCl3) δ: 6.62 (s, 2H), 4.04 (s, 2H), 3.93 (dd, 1H), 3.85 (d, 1H), 3.82 (s, 3H), 3.77 (d, 1H), 3.71 (m, 1H), 3.57 (m, 2H), 3.40 (m, 2H), 3.04 (d, 1H), 2.96 (d, 1H), 2.64 (d, 2H), 2.60 (s, 6H), 2.33-2.44 (m, 10H), 1.70 (m, 2H), 1.60 (m, 4H), 1.44 (m, 2H), 1.15 (s, 3H), 1.12 (s, 3H). LC-MS *m/z* (M+H): 595.61.

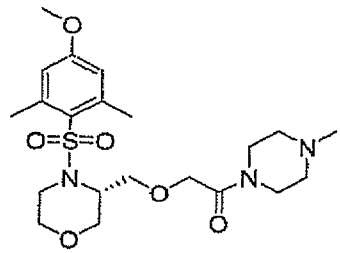
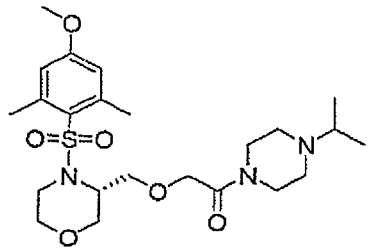
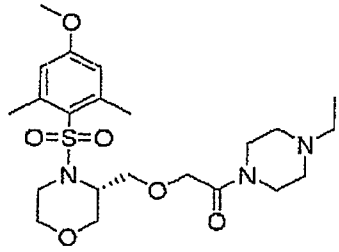
2. (R)-2-((4-(4-Methoxy-2,6-dimethylphenylsulfonyl)-6,6-dimethylmorpholin-3-yl)methoxy)-1-(4-(3-(piperidin-1-yl)propyl)piperidin-1-yl)ethanone

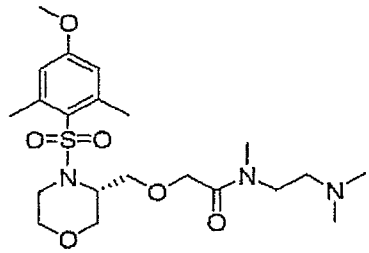
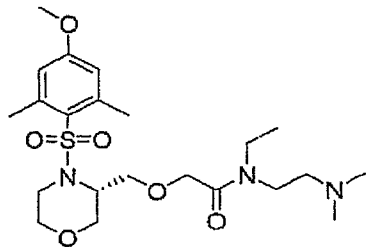
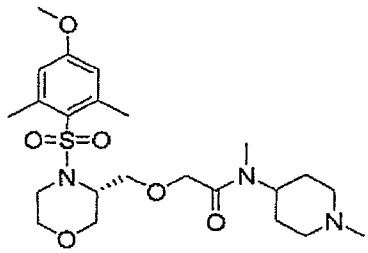
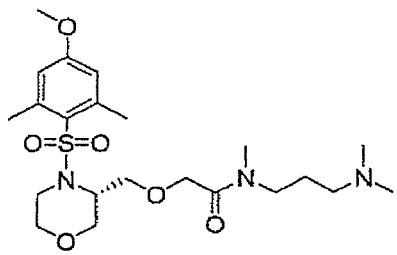
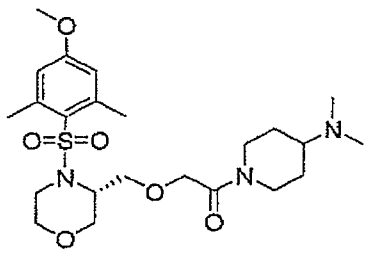
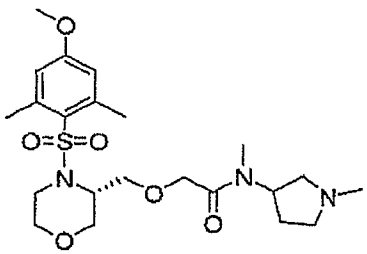


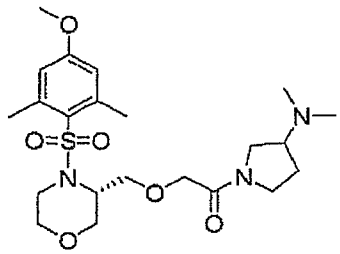
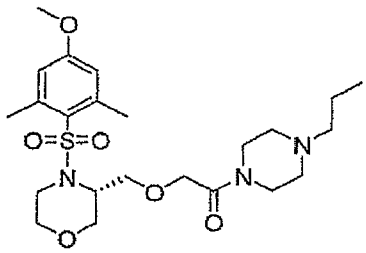
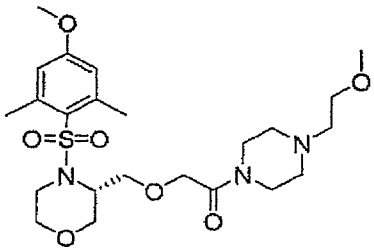
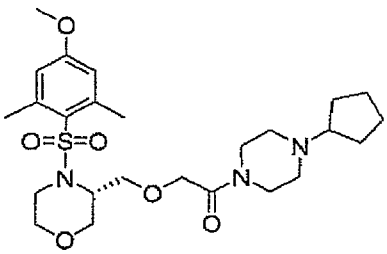
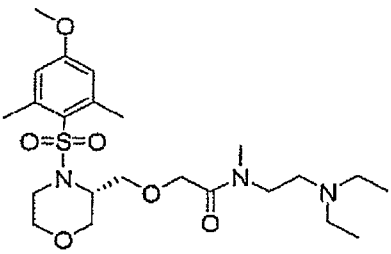
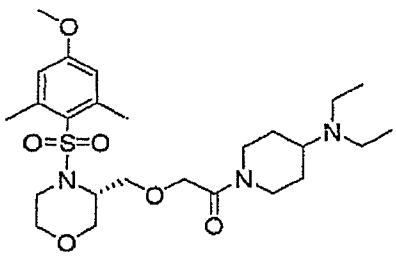
^{1}H NMR (400 MHz, CDCl3) δ: 6.62 (s, 2H), 4.48 (d, 1H), 4.02 (s, 2H), 3.93 (dd, 1H), 3.85 (d, 1H), 3.82 (s, 3H), 3.62-3.80 (m, 3H), 3.57 (m, 1H), 3.51 (m, 1H), 3.08 (t, 1H), 2.95-3.02 (m, 2H), 2.88 (d, 1H), 2.66 (d, 2H), 2.63 (s, 6H), 2.51 (m, 1H), 2.38 (m, 4H), 2.28 (m, 2H), 1.70 (br d, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.43 (m, 2H), 1.24 (m, 2H), 1.15 (s, 6H), 1.13 (m, 2H), 1.06 (m, 2H). LC-MS *m/z* (M+H): 594.25.

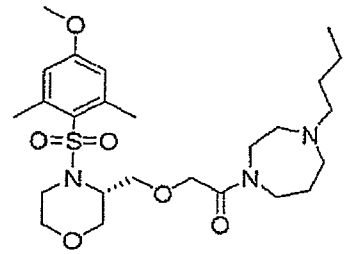
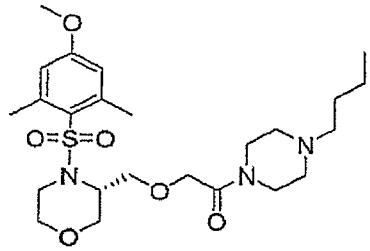
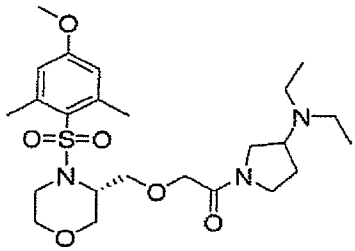
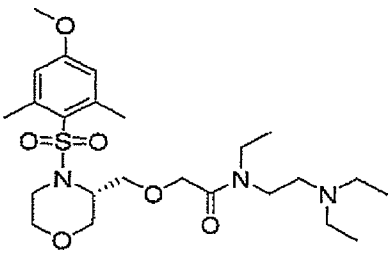
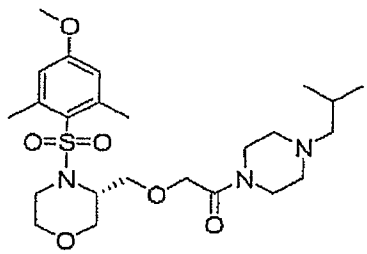
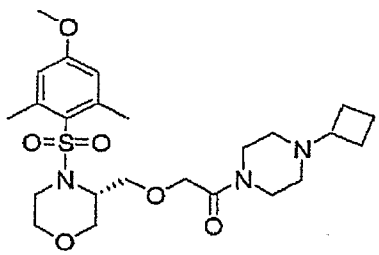
Compounds listed in Table I are prepared using methods illustrated above. All compounds in Table I exhibit an IC_{50} determined as described in Example 7 that is 5 micromolar or less. Mass spectroscopy (MS) data is provided as M+1, with retention times (Ret time) shown in minutes.

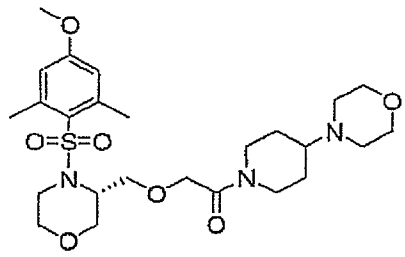
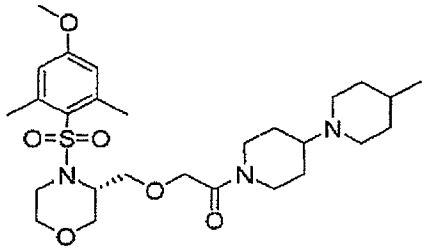
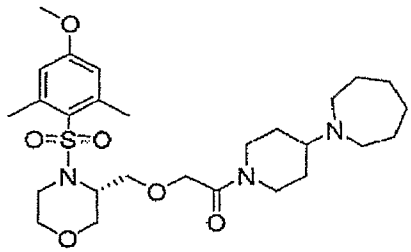
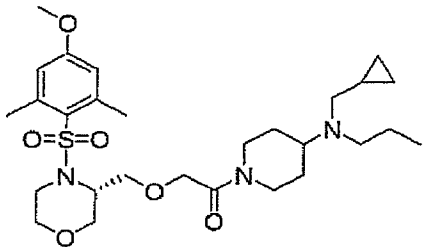
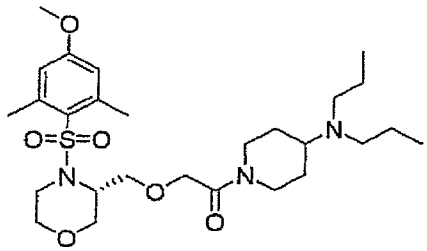
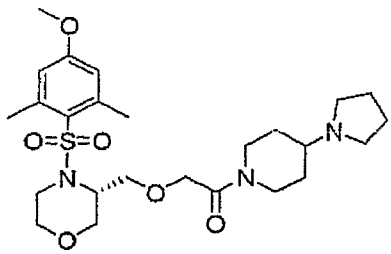
Table I
Representative Aryl Sulfonyl Heterocycles

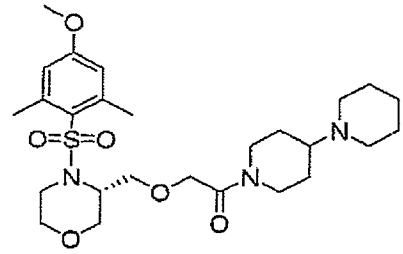
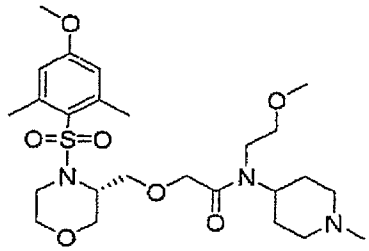
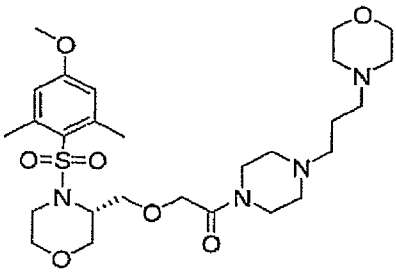
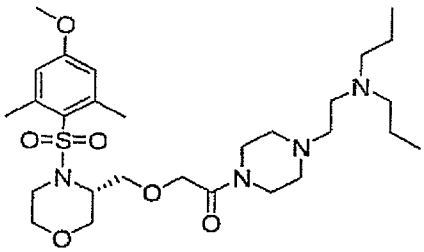
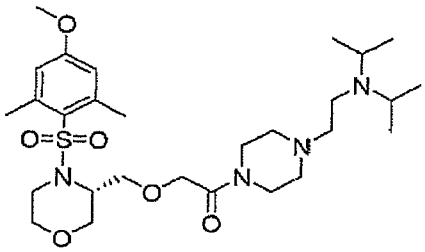
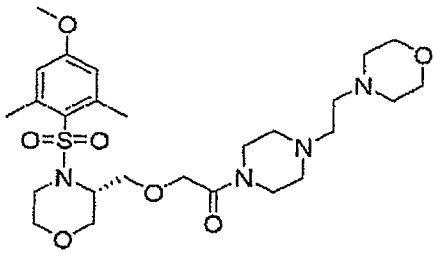
	Compound	Name	Ret Time	MS
1		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-(4-methylpiperazin-1-yl)-2-oxoethoxy]methyl}morpholine	1.15	456.31
2		(3S)-3-{[2-(4-isopropylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.15	484.35
3		(3S)-3-{[2-(4-ethylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.15	470.34

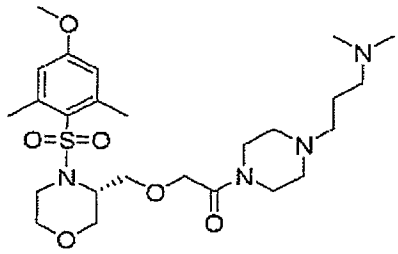
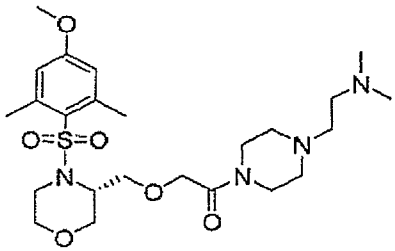
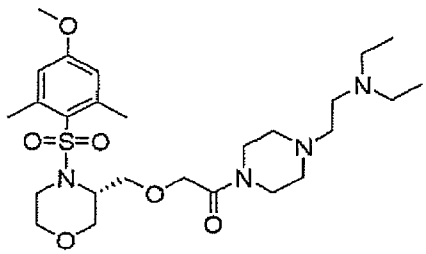
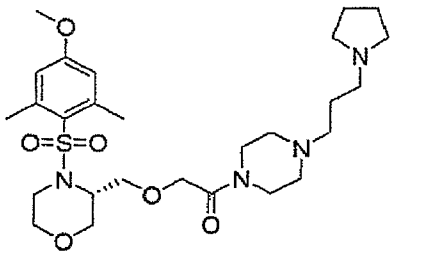
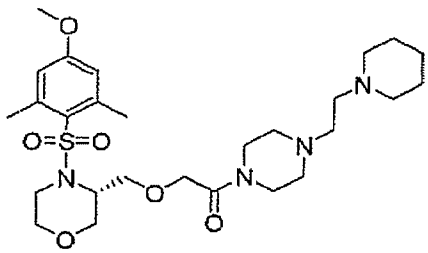
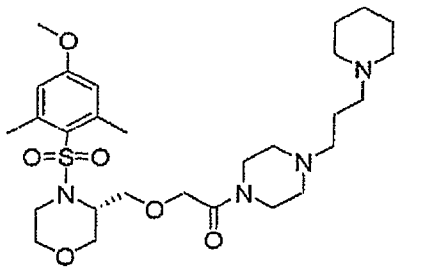
	Compound	Name	Ret Time	MS
4		N-[2-(dimethylamino)ethyl]-2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-methylacetamide	1.15	458.33
5		N-[2-(dimethylamino)ethyl]-N-ethyl-2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetamide	1.16	472.35
6		2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.15	484.37
7		N-[3-(dimethylamino)propyl]-2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-methylacetamide	1.15	472.36
8		1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-*N,N*-dimethylpiperidin-4-amine	1.15	484.37
9		2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)acetamide	1.15	470.35

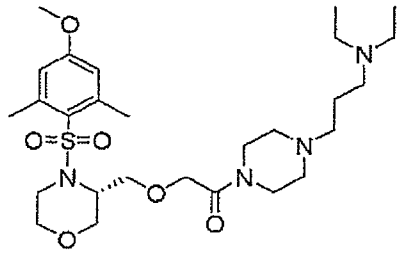
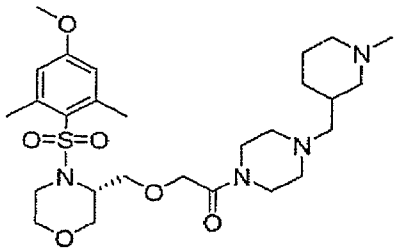
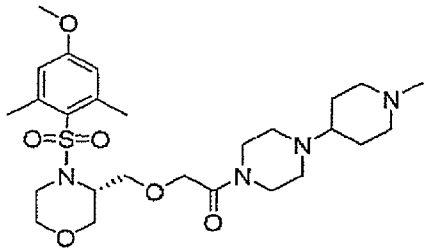
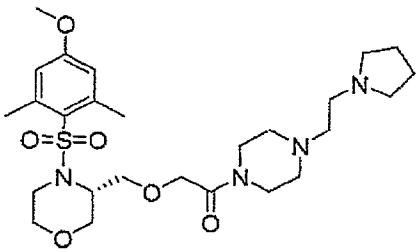
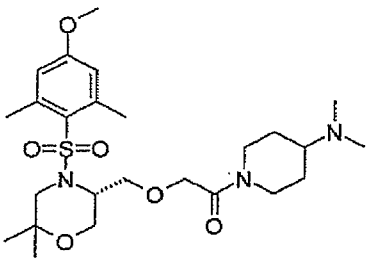
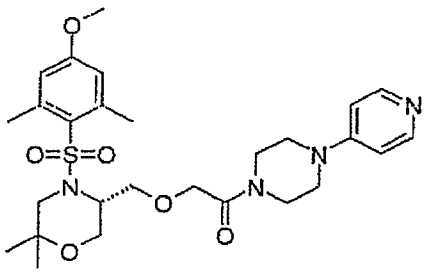
	Compound	Name	Ret Time	MS
10		1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-*N,N*-dimethylpyrrolidin-3-amine	1.14	470.37
11		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-oxo-2-(4-propylpiperazin-1-yl)ethoxy]methyl}morpholine	1.16	484.38
12		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.15	500.38
13		(3S)-3-{[2-(4-cyclopentylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.17	510.41
14		N-[2-(diethylamino)ethyl]-2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-methylacetamide	1.15	486.39
15		*N,N*-diethyl-1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperidin-4-amine	1.16	512.43

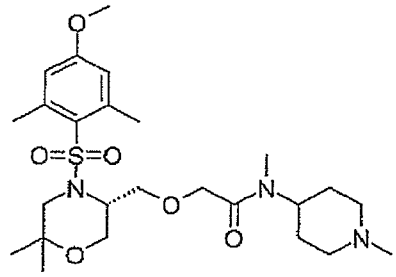
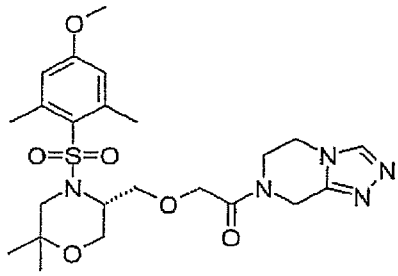
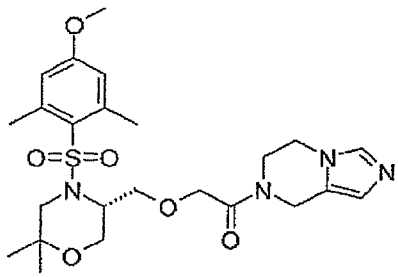
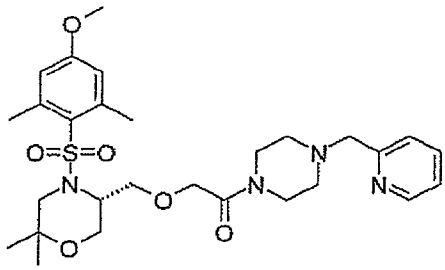
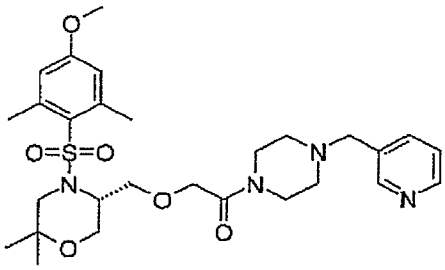
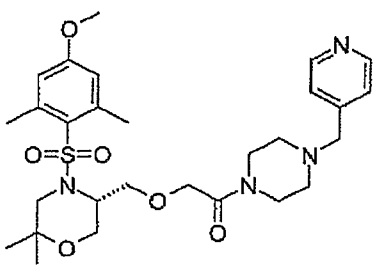
	Compound	Name	Ret Time	MS
16		1-butyl-4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-1,4-diazepane	1.17	512.43
17		(3S)-3-{[2-(4-butylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.17	498.42
18		*N,N*-diethyl-1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]pyrrolidin-3-amine	1.15	498.42
19		N-[2-(diethylamino)ethyl]-N-ethyl-2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetamide	1.17	500.43
20		(3S)-3-{[2-(4-isobutylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.16	498.42
21		(3S)-3-{[2-(4-cyclobutylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholine	1.16	496.41

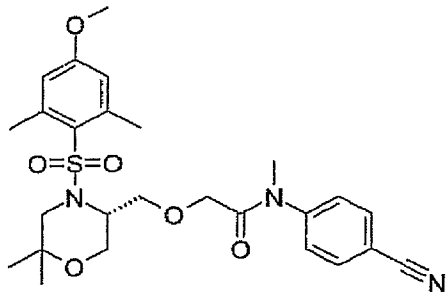
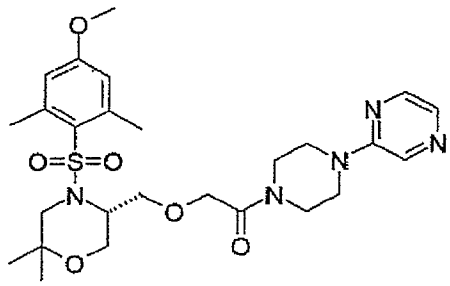
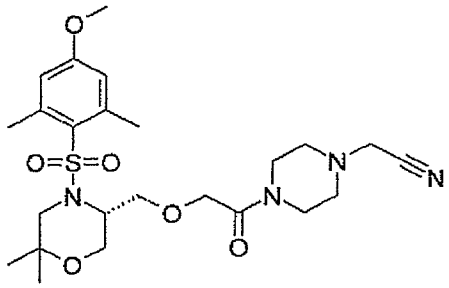
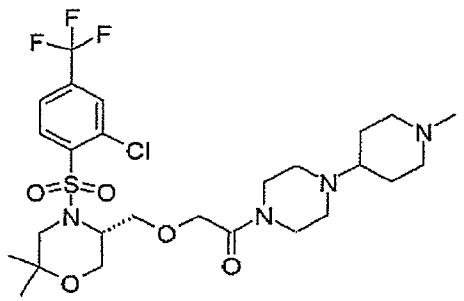
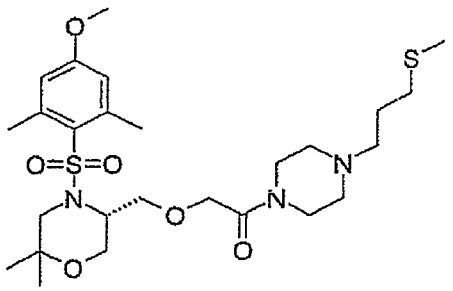
	Compound	Name	Ret Time	MS
22		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-(4-morpholin-4-ylpiperidin-1-yl)-2-oxoethoxy]methyl}morpholine	1.15	526.44
23		1'-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-4-methyl-1,4'-bipiperidine	1.18	538.47
24		1-{1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperidin-4-yl}azepane	1.17	538.47
25		N-(cyclopropylmethyl)-1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-N-propylpiperidin-4-amine	1.18	552.50
26		1-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-*N,N*-dipropylpiperidin-4-amine	1.17	540.51
27		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-oxo-2-(4-pyrrolidin-1-ylpiperidin-1-yl)ethoxy]methyl}morpholine	1.15	510.44

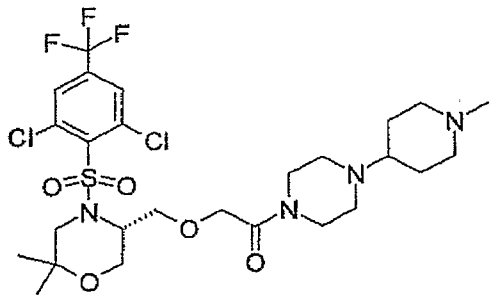
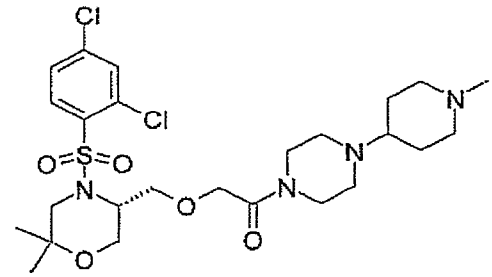
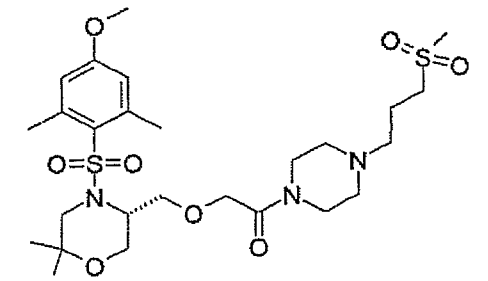
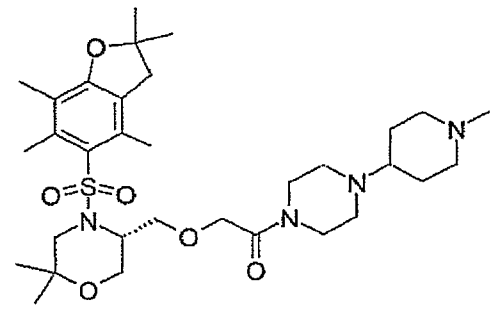
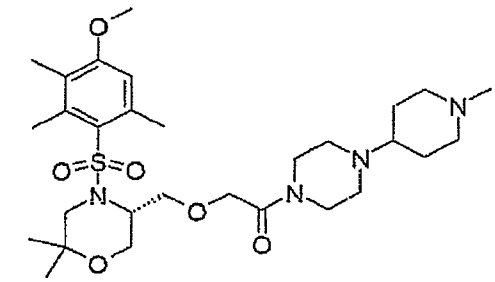
	Compound	Name	Ret Time	MS
28		1'-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]-1,4'-bipiperidine	1.16	524.46
29		2-({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)-N-(2-methoxyethyl)-N-(1-methylpiperidin-4-yl)acetamide	1.17	528.46
30		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(3-morpholin-4-ylpropyl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine		
31		N-(2-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethyl)-N-propylpropan-1-amine	1.16	569.54
32		N-isopropyl-N-(2-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethyl)propan-2-amine	1.15	569.54
33		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.14	555.50

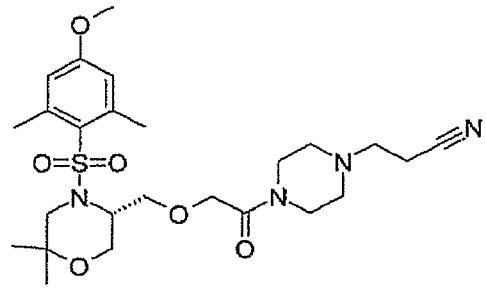
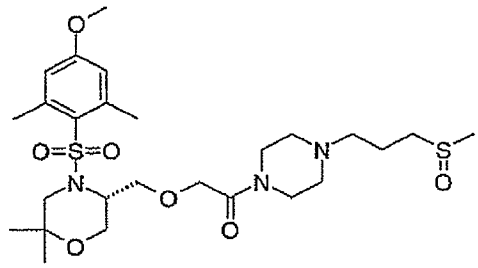
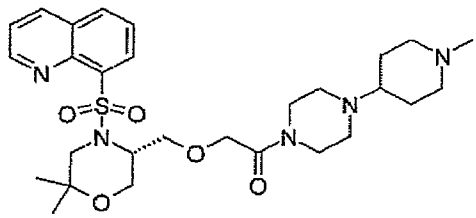
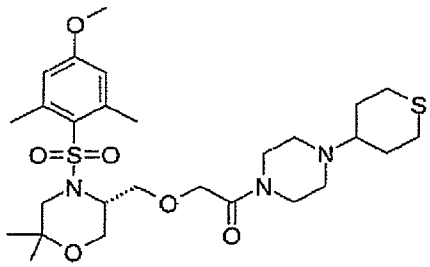
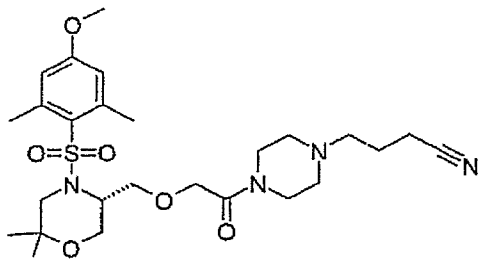
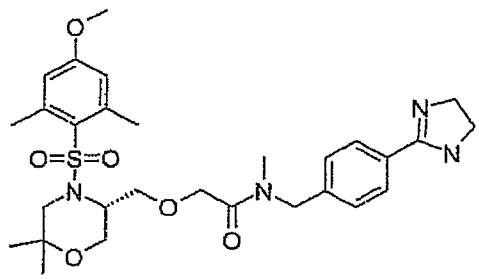
	Compound	Name	Ret Time	MS
34		3-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylpropan-1-amine	1.11	527.49
35		2-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylethanamine	1.14	513.47
36		*N,N*-diethyl-2-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethanamine	1.14	541.51
37		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.12	553.52
38		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(2-piperidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.14	553.52
39		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.13	567.54

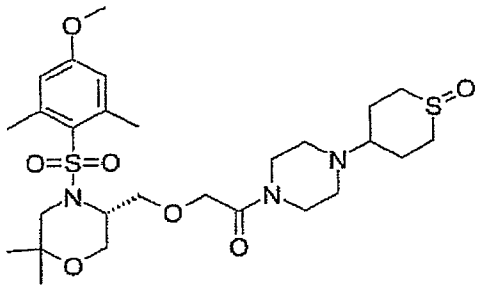
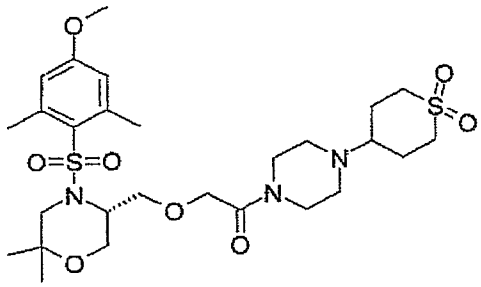
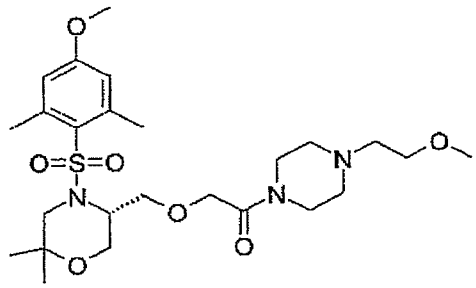
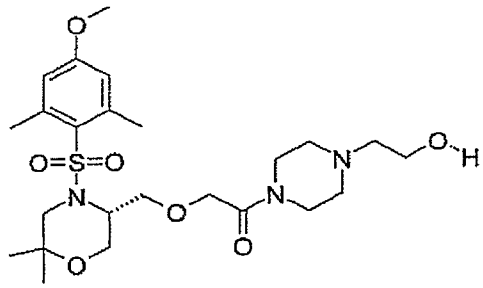
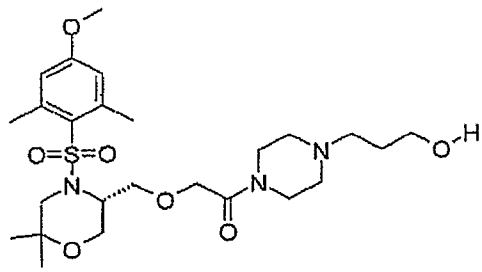
	Compound	Name	Ret Time	MS
40		*N,N*-diethyl-3-{4-[({(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]morpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propan-1-amine	1.12	555.54
41		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-[(2-{4-[(1-methylpiperidin-3-yl)methyl]piperazin-1-yl}-2-oxoethoxy)methyl]morpholine	1.12	553.53
42		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.12	539.51
43		(3S)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.14	539.50
44		1-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]-N,N-dimethylpiperidin-4-amine	1.1	512.4
45		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-{[2-oxo-2-(4-pyridin-4-ylpiperazin-1-yl)ethoxy]methyl}morpholine	1.1	547.4

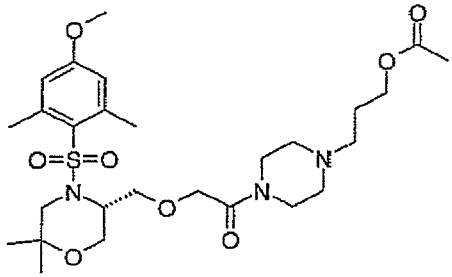
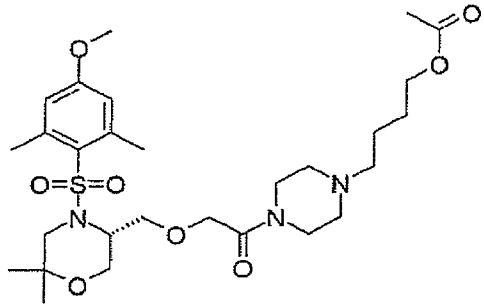
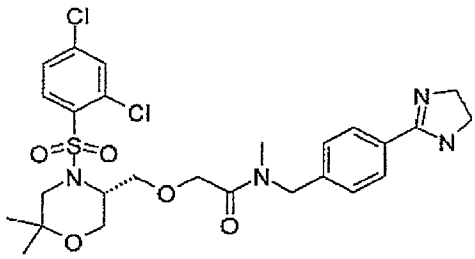
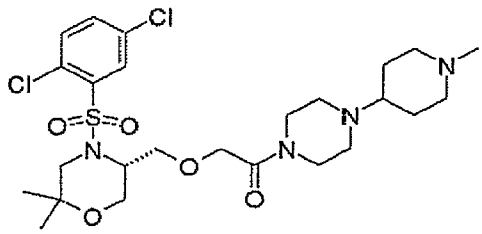
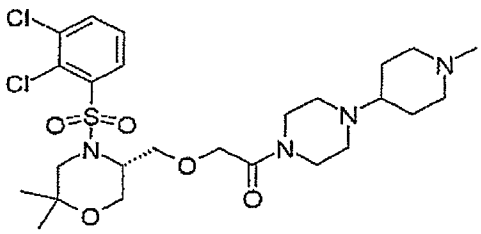
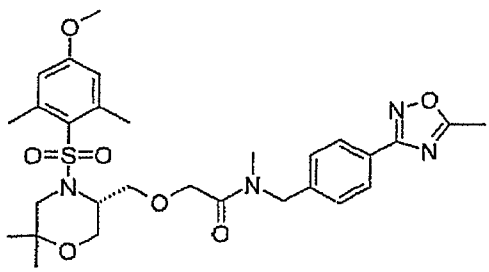
	Compound	Name	Ret Time	MS
46		2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.1	512.4
47		7-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-a]pyrazine	1.1	508.1
48		7-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine	1.1	507.1
49		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-oxo-2-[4-(pyridin-2-ylmethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.1	561.1
50		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-oxo-2-[4-(pyridin-3-ylmethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.1	561.2
51		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-oxo-2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.1	561.2

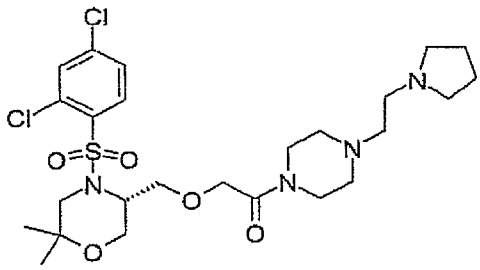
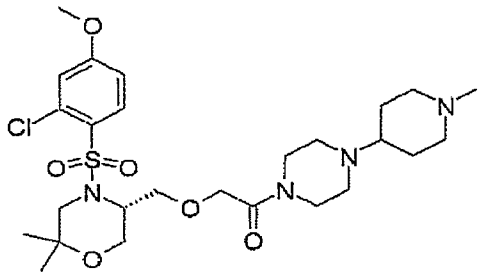
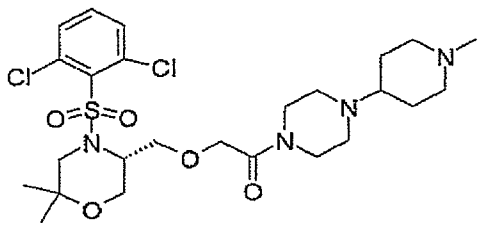
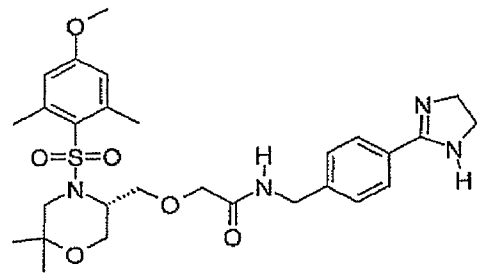
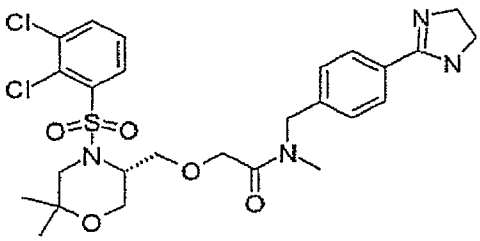
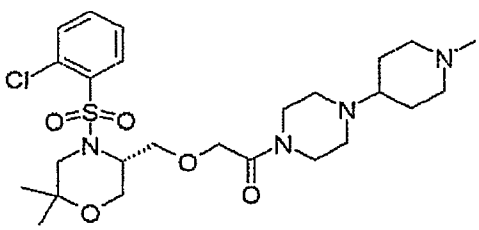
	Compound	Name	Ret Time	MS
52		N-(4-cyanophenyl)-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methylacetamide	1.2	516.2
53		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-{[2-oxo-2-(4-pyrazin-2-ylpiperazin-1-yl)ethoxy]methyl}morpholine	1.2	548.1
54		{4-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}acetonitrile	1.2	509.1
55		4-{[2-chloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	611.1
56		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-[(2-{4-[3-(methylthio)propyl]piperazin-1-yl}-2-oxoethoxy)methyl]morpholine	1.1	558.2

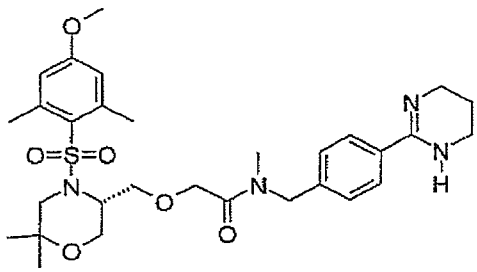
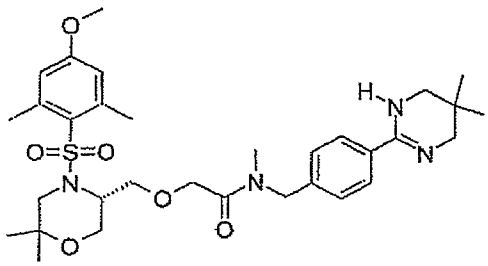
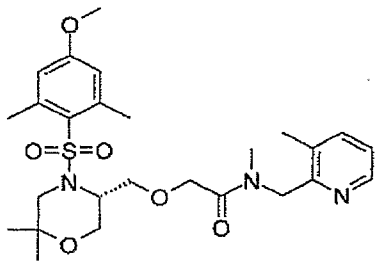
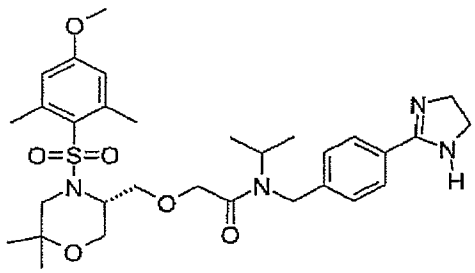
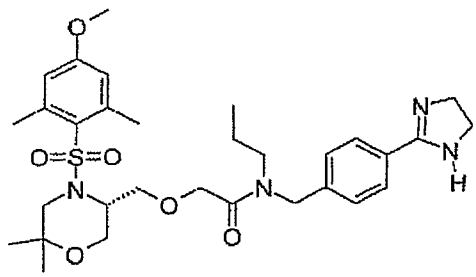
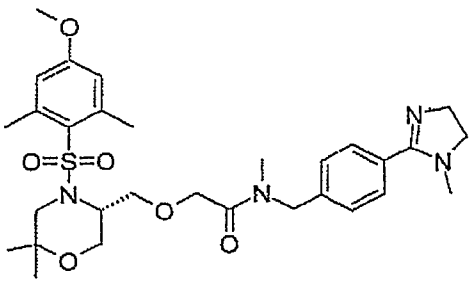
	Compound	Name	Ret Time	MS
57		4-{[2,6-dichloro-4-(trifluoromethyl)phenyl]sulfonyl}-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	645.1
58		4-[(2,4-dichlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	577.1
59		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-[(2-{4-[3-(methylsulfonyl)propyl]piperazin-1-yl}-2-oxoethoxy)methyl]morpholine	1.1	590.1
60		2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)-4-[(2,2,4,6,7-pentamethyl-2,3-dihydro-1-benzofuran-5-yl)sulfonyl]morpholine	1.2	621.2
61		4-[(4-methoxy-2,3,6-trimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	580.3

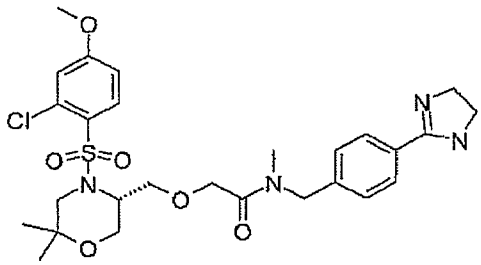
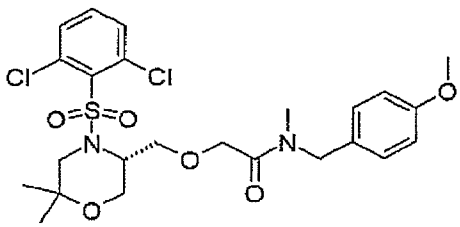
	Compound	Name	Ret Time	MS
62		3-{4-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propanenitrile	1.1	523.3
63		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-[(2-{4-[3-(methylsulfinyl)propyl]piperazin-1-yl}-2-oxoethoxy)methyl]morpholine	1.1	574.1
64		8-{[2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholin-4-yl]sulfonyl}quinoline	1.0	560.2
65		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-oxo-2-[4-(tetrahydro-2H-thiopyran-4-yl)piperazin-1-yl]ethoxy}methyl)morpholine	1.1	570.2
66		4-{4-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}butanenitrile	1.1	537.2
67		N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methylacetamide	1.1	573.3

	Compound	Name	Ret Time	MS
68		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-oxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	586.2
69		(5R)-5-({2-[4-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-2,2-dimethylmorpholine	1.1	602.1
70		(5R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-5-({2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethoxy}methyl)-2,2-dimethylmorpholine	1.1	528.2
71		2-{4-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethanol	1.1	514.2
72		3-{4-[({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propan-1-ol	1.1	528.2

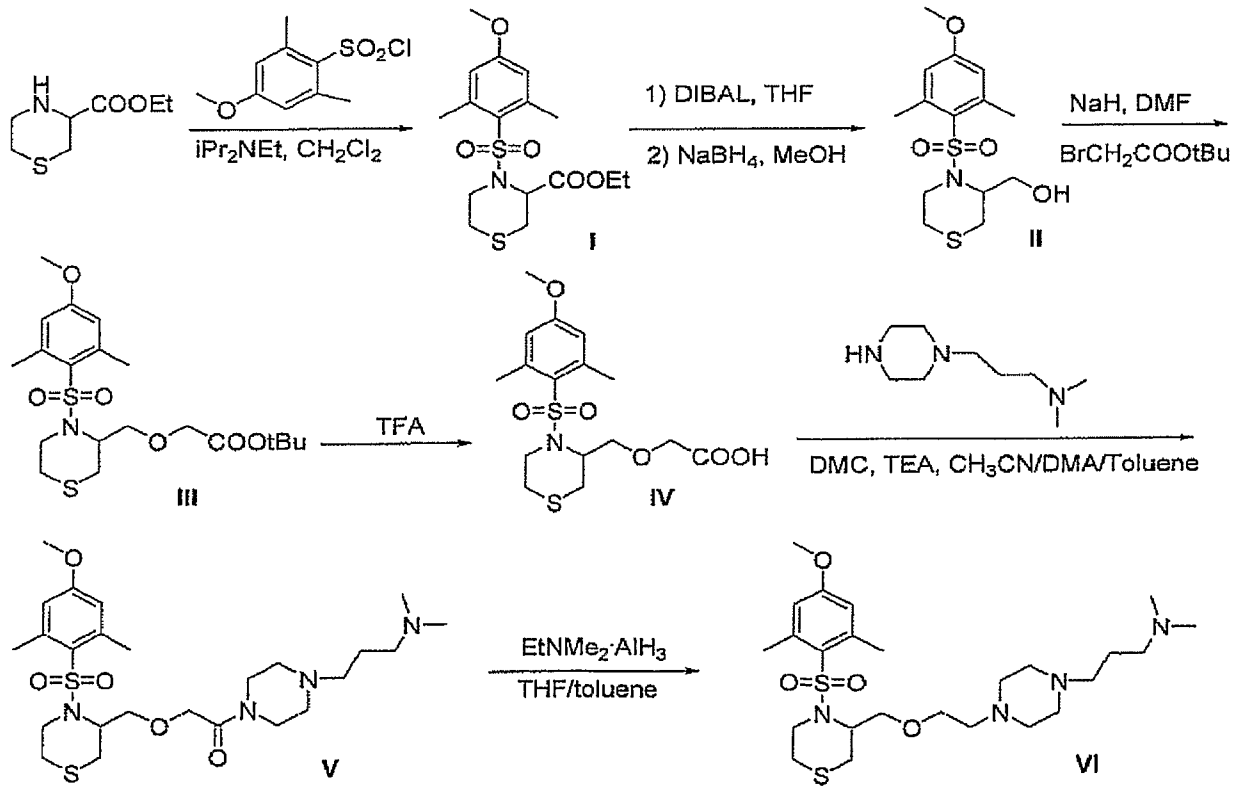
	Compound	Name	Ret Time	MS
73		3-{4-[2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propyl acetate	1.1	570.2
74		4-{4-[2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}butyl acetate	1.2	584.2
75		2-({4-[(2,4-dichlorophenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-methylacetamide	1.2	583.0
76		4-[(2,5-dichlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	577.1
77		4-[(2,3-dichlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	577.1
78		2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methyl-N-[4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl]acetamide	1.3	587.1

	Compound	Name	Ret Time	MS
79		4-[(2,4-dichlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)morpholine	1.2	577.2
80		4-[(2-chloro-4-methoxyphenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	573.3
81		4-[(2,6-dichlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	577.2
82		N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetamide	1.1	559.3
83		2-({4-[(2,3-dichlorophenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-methylacetamide	1.2	583.2
84		4-[(2-chlorophenyl)sulfonyl]-2,2-dimethyl-5-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)morpholine	1.1	543.2

	Compound	Name	Ret Time	MS
85		2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methyl-N-[4-(1,4,5,6-tetrahydropyrimidin-2-yl)benzyl]acetamide	1.2	587.2
86		N-[4-(5,5-dimethyl-1,4,5,6-tetrahydropyrimidin-2-yl)benzyl]-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methylacetamide	1.2	615.3
87		2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methyl-N-[(3-methylpyridin-2-yl)methyl]acetamide	1.2	520.3
88		N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-isopropyl-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)acetamide	1.1	601.4
89		N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-propylacetamide	1.1	601.4
90		2-({(3R)-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-methyl-N-[4-(1-methyl-4,5-dihydro-1H-imidazol-2-yl)benzyl]acetamide	1.2	587.1

	Compound	Name	Ret Time	MS
91		2-({4-[(2-chloro-4-methoxyphenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-[4-(4,5-dihydro-1H-imidazol-2-yl)benzyl]-N-methylacetamide	1.2	579.0
92		2-({4-[(2,6-dichlorophenyl)sulfonyl]-6,6-dimethylmorpholin-3-yl}methoxy)-N-(4-methoxybenzyl)-N-methylacetamide	1.3	545

E. 93 3-{4-[({4-[(4-METHOXY-2,6-DIMETHYLPHENYL)SULFONYL]THIOMORPHOLIN-3-YL}M94ETHOXY)ACETYL] PIPERAZIN-1-YL}-*N,N*-DIMETHYLPROPAN-1-AMINE



Step 1. [4-(4-Methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine-3-carboxylic acid ethyl ester (I)

To a solution of thiomorpholine-3-carboxylic acid ethyl ester (2.0 g, 11.4 mmol) in anhydrous CH_2Cl_2 (25 mL) under N_2 at 0 °C is added diisopropylethylamine (2.98 mL, 17.1 mmol), followed by 4-methoxy-2, 6-dimethylphenylsulfonyl chloride. The mixture is stirred at rt overnight. The reaction mixture is washed with aq. 1N HCl and brine, dried over Na_2SO_4 and concentrated under reduced

pressure. The residue is purified by silica gel chromatography (hexane/EtOAc: 4/1) to afford compound **I** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.75 (t, 1H), 4.20 (q, 2H), 3.83 (m, 1H), 3.81 (s, 3H), 3.55 (m, 1H), 3.15 (m, 1H), 3.02 (m, 1H), 2.90 (m, 1H), 2.61 (s, 6H), 2.32 (m, 1H), 1.25 (t, 3H). LC-MS *m/z* (M+H): 373.87.

Step 2. {4-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}-methanol (**II**)

To a solution of compound **I** (2.50 g, 6.7 mmol) in anhydrous THF (50 mL) under N_2 at rt is added DIBAL (1M/THF, 33.5 mL, 33.5 mmol). After stirring for 2 h at rt, the reaction is quenched with $Na_2SO_4{\cdot}10H_2O$, filtered through celite and concentrated under reduced pressure. The residue is dissolved in MeOH (50 mL), and treated with $NaBH_4$ (190 mg, 5 mmol) at rt for 30 min. The reaction is quenched with ½ saturated $NaHCO_3$, and MeOH is removed under reduced pressure. The residue is extracted with EtOAc. The organic layer is washed with 1N NaOH and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is purified by passing through a silica gel plug (hexane/EtOAc: 2/1) to afford compound **II** as a colorless oil. LC-MS *m/z* (M+H): 332.00.

Step 3. {4-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-ylmethoxy}-acetic acid *tert*-butyl ester (**III**)

To a solution of compound **II** (1.84 g, 5.56 mmol) in anhydrous DMF (30 mL) at 0 °C is added NaH (60% in mineral oil, 0.27 g, 6.67 mmol), followed by *tert*-butyl bromoacetate (1.24 mL, 8.40 mmol). The mixture is then warmed to rt, and stirred overnight. The reaction mixture is diluted with EtOAc, washed with water (3x) and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue is purified by silica gel chromatography (hexane/EtOAc: 4/1) to afford compound **III** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.17 (t, 1H), 4.03 (m, 1H), 3.87 (m, 2H), 3.79-3.84 (m, 4H), 3.69 (m, 1H), 3.22 (m, 1H), 3.09 (m, 1H), 2.74-2.82 (m, 2H), 2.60 (s, 6H), 2.33 (m, 1H), 1.46 (s, 9H). LC-MS *m/z* (M+Na): 468.03

Step 4. {[4-(4-Methoxy-2, 6-dimethylphenyl)sulfonyl]thiomorpholin-3-ylmethoxy}-acetic acid (**IV**)

Compound **III** (1.42 g, 3.19 mmol) is treated with TFA (8 mL) at rt overnight. TFA is removed under reduced pressure. The residue is purified by flash chromatography (EtOAc/hexane: 1/1) to afford compound **IV** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.66 (s, 2H), 4.46 (m, 1H), 4.19-4.25 (m, 2H), 4.06 (m, 1H), 3.83 (s, 3H), 3.81 (m, 1H), 3.46 (m, 1H), 3.27 (m, 1H), 3.13 (m, 1H), 2.62 (s, 6H), 2.55-2.59 (m, 2H), 2.33 (m, 1H). LC-MS *m/z* (M+H): 389.80

Step 5. 3-{4-[({4-[(4-Methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl] piperazin-1-yl}-*N,N*-dimethylpropan-1-amine (**V**)

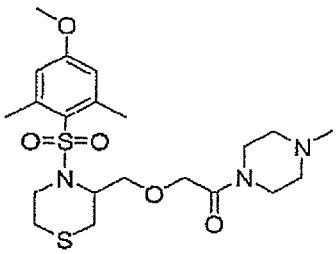
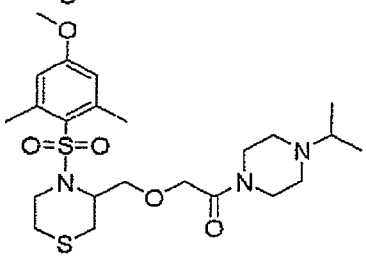
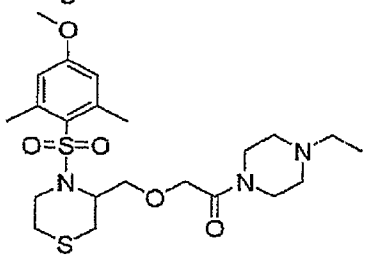
To a solution of compound **IV** (46.7 mg, 0.12 mmol) in anhydrous DMA (0.6 mL) is added dimethyl-(3-piperazin-1-yl-propyl)-amine (0.1 mmol, 0.2 M in toluene), DMC (0.2 mmol, 0.2 M in anhydrous CH_3CN) and TEA (0.25 mmol, 1M in toluene). The mixture is heated at 50 °C for 3 h.

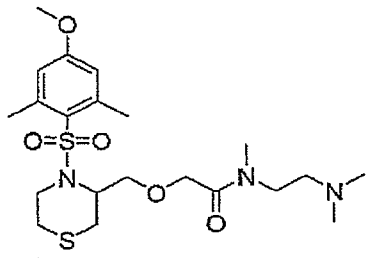
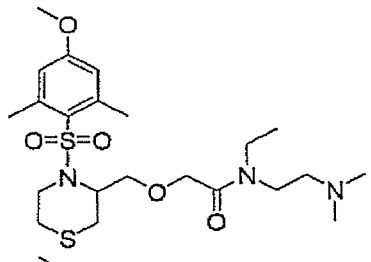
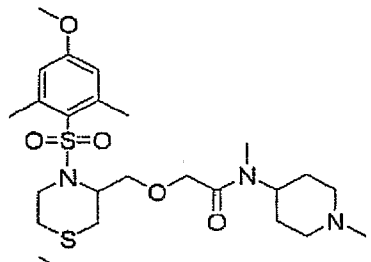
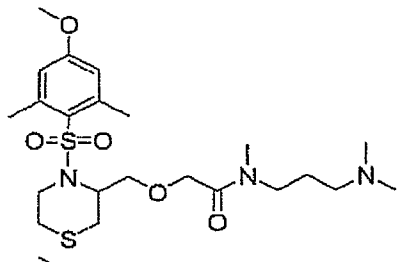
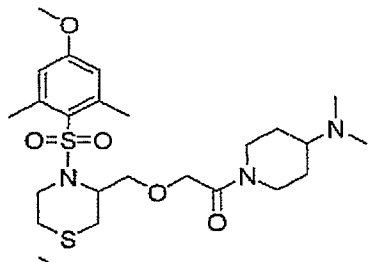
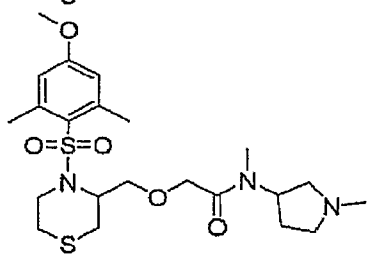
The reaction mixture is cooled to rt, and concentrated under reduced pressure. The residue is partitioned between EtOAc and 1N NaOH, organic layer is separated, loaded onto SCX cartridge (3 g of resin) which are pre-washed with MeOH (9 mL), and eluted with MeOH (2 x 9 mL) to remove non-basic impurities, and EtOAc/MeOH/TEA (5/5/2, 9 mL) to afford compound V as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.01-4.17 (m, 4H), 3.81 (s, 3H), 3.79 (m, 1H), 3.65 (m, 1H), 3.55-3.61 (m, 2H), 3.36-3.40 (m, 2H), 3.20 (m, 1H), 3.08 (m, 1H), 2.64-2.81 (m, 2H), 2.58 (s, 6H), 2.22-2.40 (m, 15H), 1.64-1.72 (m, 2H). LC-MS *m/z* (M+H): 543.15.

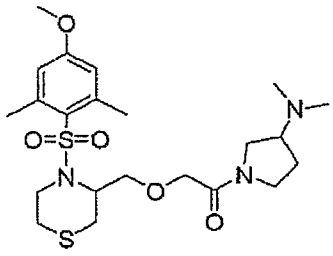
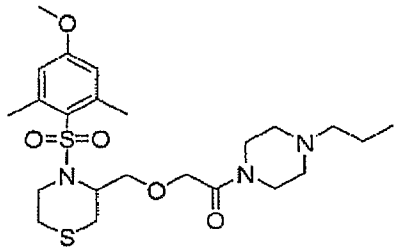
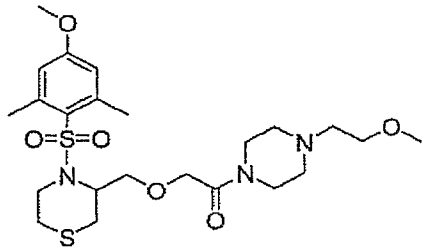
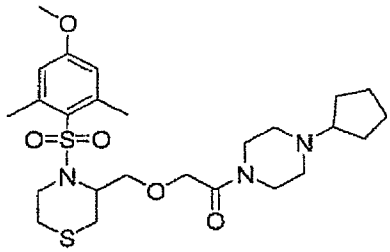
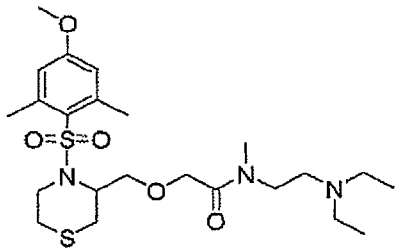
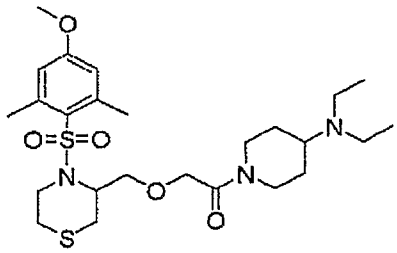
F. ADDITIONAL ARYL SULFONYL HETEROCYCLES

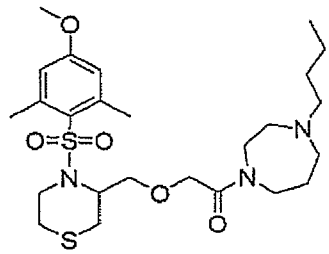
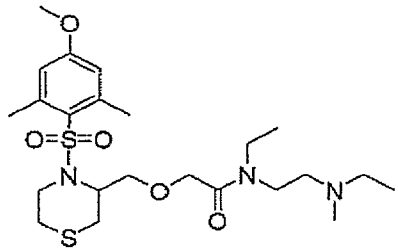
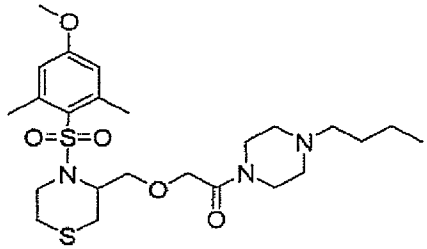
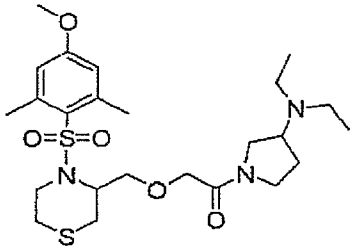
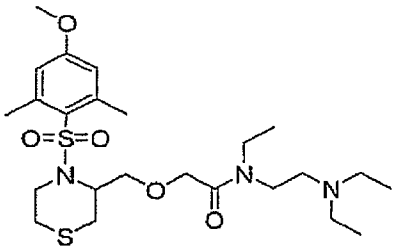
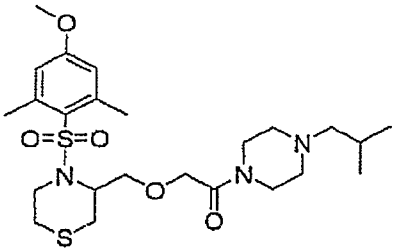
Using routine modifications of the methods illustrated above, the starting materials may be varied and additional steps employed to produce other aryl sulfonyl heterocycles. Compounds listed in Table II are prepared using such methods. All compounds in Table II exhibit an IC_{50} determined as described in Example 7 that is 5 micromolar or less. Mass spectroscopy (MS) data is provided as M+1, with retention times (Ret time) are shown in minutes.

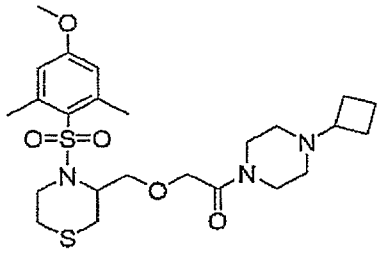
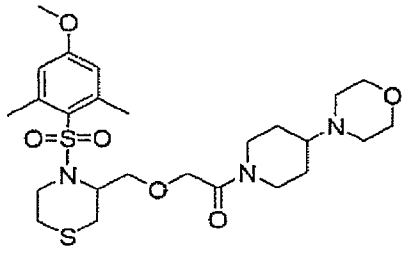
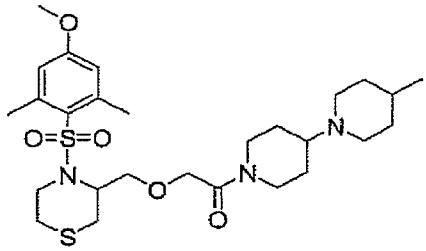
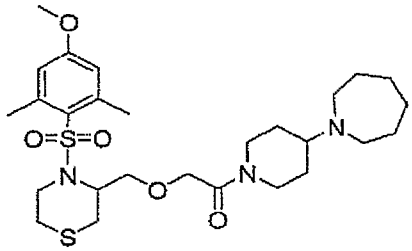
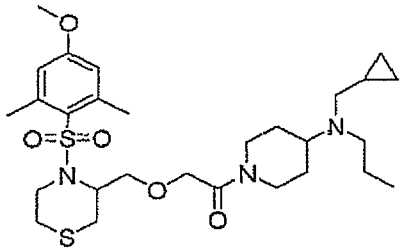
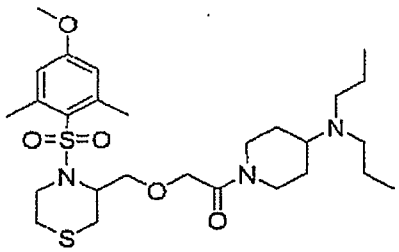
Table II
Representative Aryl Sulfonyl Heterocycles

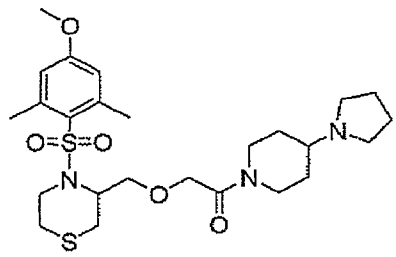
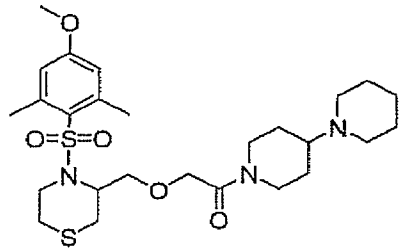
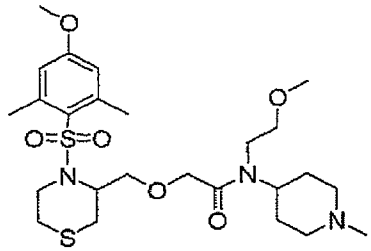
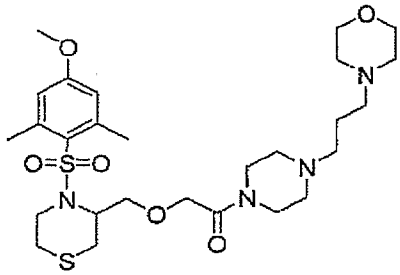
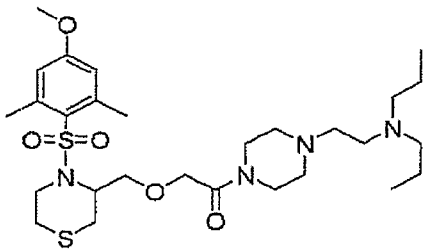
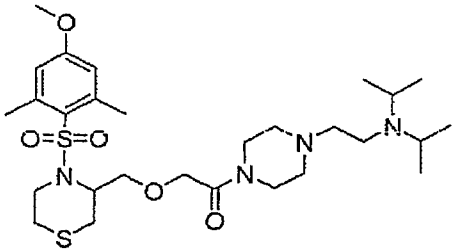
Compound	Name	Ret Time	MS
93 	4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-(4-methylpiperazin-1-yl)-2-oxoethoxy]methyl}thiomorpholine	1.17	472.39
94 	3-{[2-(4-isopropylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.18	500.43
95 	3-{[2-(4-ethylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.17	486.41

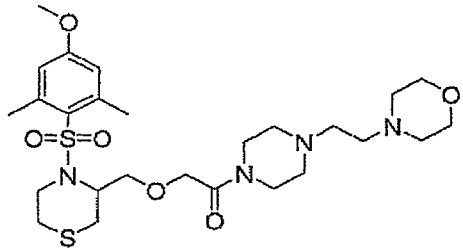
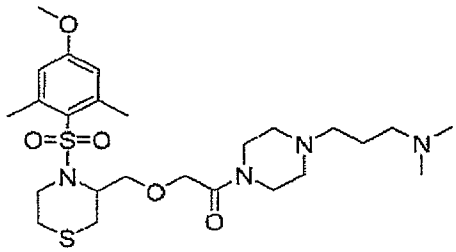
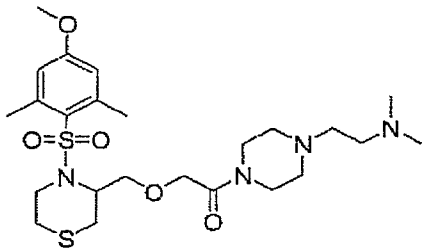
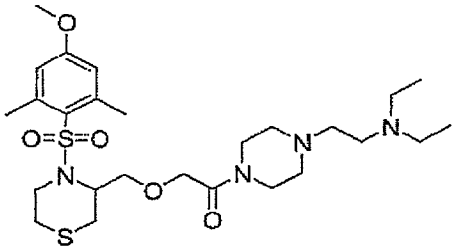
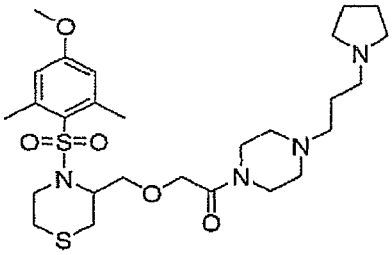
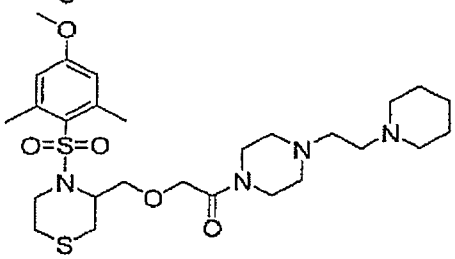
	Compound	Name	Ret Time	MS
96		N-[2-(dimethylamino)ethyl]-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-methylacetamide	1.18	474.40
97		N-[2-(dimethylamino)ethyl]-N-ethyl-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetamide	1.19	488.42
98		2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.17	500.43
99		N-[3-(dimethylamino)propyl]-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-methylacetamide	1.18	488.42
100		1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-*N,N*-dimethylpiperidin-4-amine	1.17	500.43
101		2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)acetamide	1.17	486.41

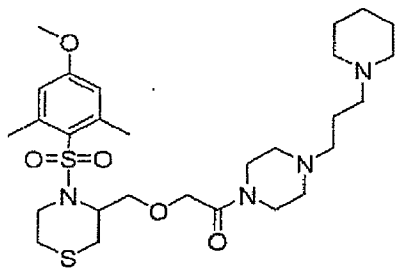
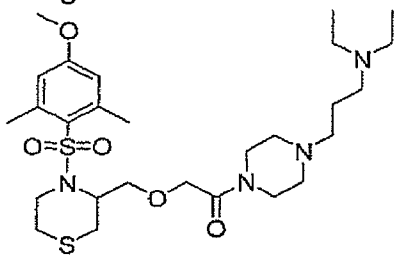
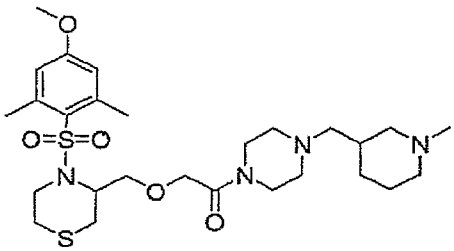
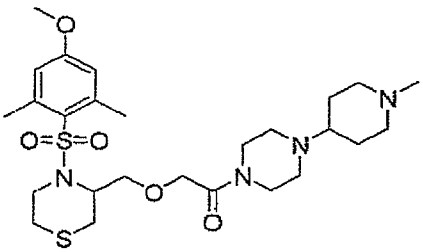
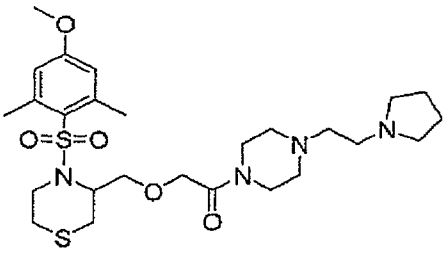
	Compound	Name	Ret Time	MS
102		1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-*N,N*-dimethylpyrrolidin-3-amine	1.16	486.42
103		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-oxo-2-(4-propylpiperazin-1-yl)ethoxy]methyl}thiomorpholine	1.18	500.44
104		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethoxy}methyl)thiomorpholine	1.18	516.43
105		3-{[2-(4-cyclopentylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.2	526.46
106		N-[2-(diethylamino)ethyl]-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-methylacetamide	1.19	502.50
107		*N,N*-diethyl-1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperidin-4-amine	1.18	528.48

	Compound	Name	Ret Time	MS
108		1-butyl-4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-1,4-diazepane	1.2	528.48
109		N-ethyl-N-{2-[ethyl(methyl)amino]ethyl}-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetamide	1.19	502.45
110		3-{[2-(4-butylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.2	514.46
111		*N,N*-diethyl-1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]pyrrolidin-3-amine	1.18	514.46
112		N-[2-(diethylamino)ethyl]-N-ethyl-2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetamide	1.2	516.48
113		3-{[2-(4-isobutylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.2	514.46

	Compound	Name	Ret Time	MS
114		3-{[2-(4-cyclobutylpiperazin-1-yl)-2-oxoethoxy]methyl}-4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholine	1.18	512.44
115		4-{1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperidin-4-yl}morpholine	1.18	542.48
116		1'-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-4-methyl-1,4'-bipiperidine	1.2	554.51
117		1-{1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperidin-4-yl}azepane	1.2	554.51
118		N-(cyclopropylmethyl)-1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-N-propylpiperidin-4-amine	1.21	568.53
119		1-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-*N,N*-dipropylpiperidin-4-amine	1.2	556.52

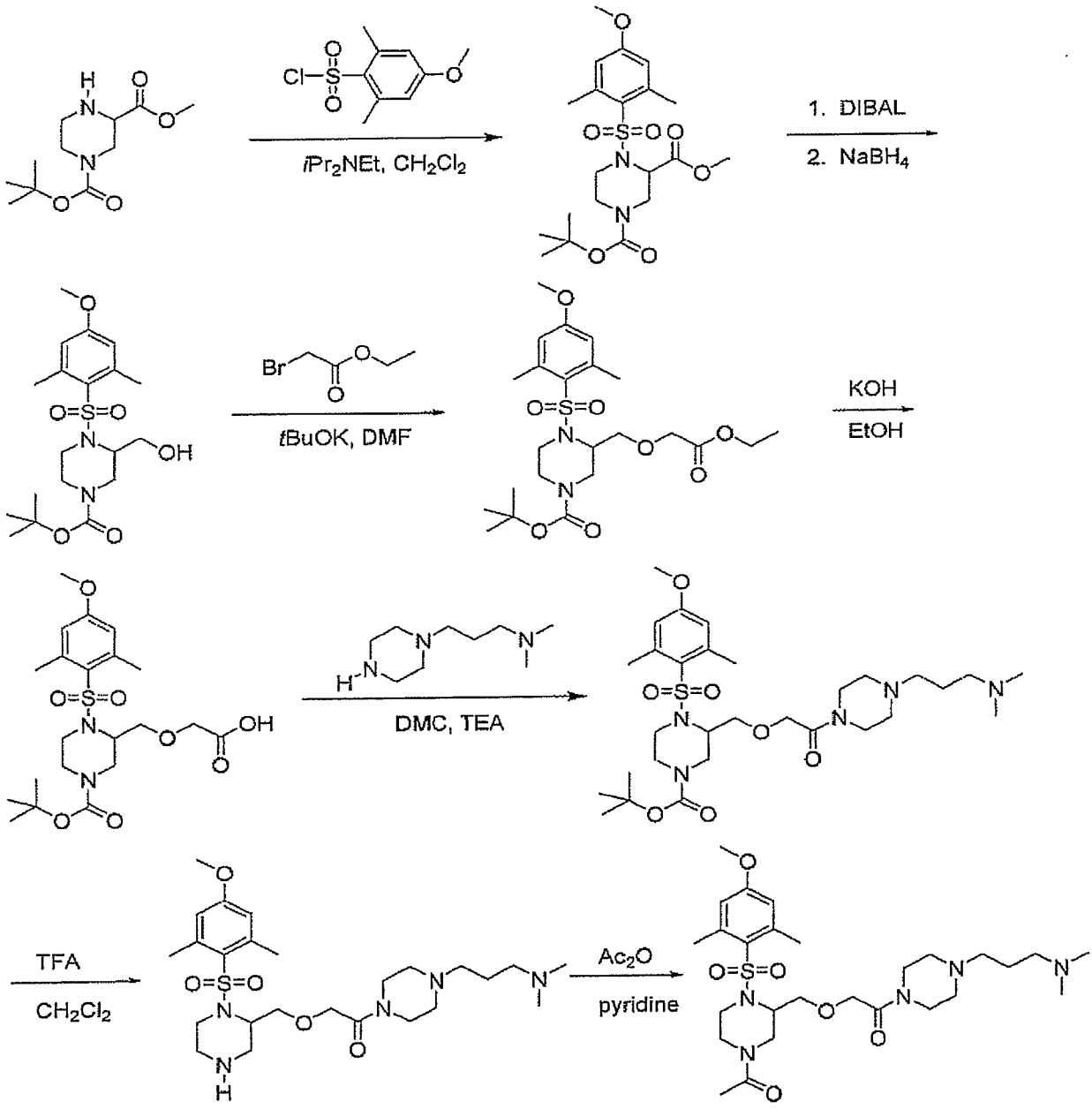
	Compound	Name	Ret Time	MS
120		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-{[2-oxo-2-(4-pyrrolidin-1-ylpiperidin-1-yl)ethoxy]methyl}thiomorpholine	1.18	526.47
121		1'-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]-1,4'-bipiperidine	1.18	540.49
122		2-({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)-N-(2-methoxyethyl)-N-(1-methylpiperidin-4-yl)acetamide	1.2	544.49
123		4-(3-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propyl)morpholine		
124		N-(2-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethyl)-N-propylpropan-1-amine	1.2	585.57
125		N-isopropyl-N-(2-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethyl)propan-2-amine	1.18	585.57

	Compound	Name	Ret Time	MS
126		4-(2-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethyl)morpholine	1.17	571.52
127		3-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylpropan-1-amine	1.14	543.51
128		2-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylethanamine	1.17	529.49
129		*N,N*-diethyl-2-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}ethanamine	1.17	557.53
130		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)thiomorpholine	1.15	569.53
131		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(2-piperidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)thiomorpholine	1.17	569.54

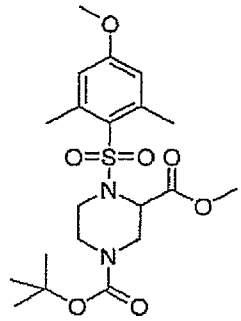
	Compound	Name	Ret Time	MS
132		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)thiomorpholine	1.15	583.56
133		*N,N*-diethyl-3-{4-[({4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]thiomorpholin-3-yl}methoxy)acetyl]piperazin-1-yl}propan-1-amine	1.15	571.55
134		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-[(2-{4-[(1-methylpiperidin-3-yl)methyl]piperazin-1-yl}-2-oxoethoxy)methyl]thiomorpholine	1.14	569.54
135		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)thiomorpholine	1.15	555.52
136		4-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-3-({2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)thiomorpholine	1.18	555.51

EXAMPLE 2. SYNTHESIS OF REPRESENTATIVE ARYL SULFONYL HETEROCYCLES

A. 2-[4-ACETYL-1-(4-METHOXY-2,6-DIMETHYLBENZENESULFONYL) PIPERAZIN-2-YLMETHOXY]-1-[4-(3-DIMETHYLAMINOPROPYL)PIPAZIN-1-YL]ETHANONE

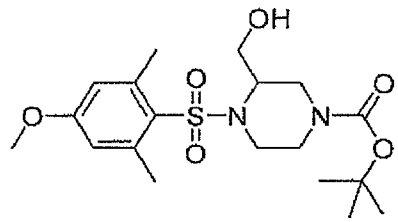


Step 1. 4-(4-Methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester



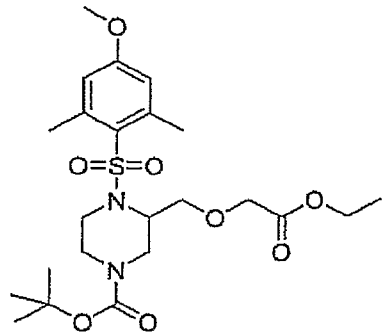
The title compound as a yellow oil is prepared as indicated above using piperazine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.63 (s, 2H), 4.53 (m, 1H), 4.40 (m, 1H), 4.11 (m, 1H), 3.82 (s, 3H), 3.69 (s, 3H), 3.55 (m, 1H), 3.42 (m, 1H), 3.17 (m, 1H), 2.86 (m, 1H), 2.61 (s, 6H), 1.43 (s, 9H). LC-MS *m/z* ($M + Na^+$): 466.

Step 2. 3-Hydroxymethyl-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester



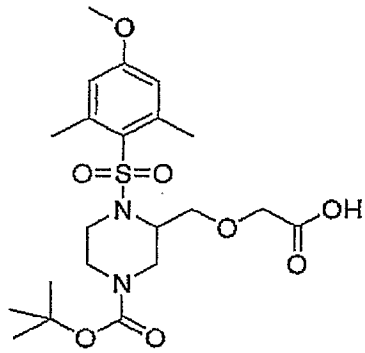
A 1.5 M solution of DIBAL in toluene (12.1 mL, 18.2 mmol) is added dropwise to a solution of 4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (3.22 g, 7.28 mmol) and CH_2Cl_2 (70 mL) at –78 °C under nitrogen. After stirring for 1 h at –78 °C, the bath is thawed to 0 °C over 1 h. The excess DIBAL is quenched with EtOAc, the cold bath is removed, and then a 15% solution of sodium potassium tartrate (80 mL) is added. The mixture is vigorously stirred overnight. The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (2 x 75 mL). The combined organics are dried over Na_2SO_4, filtered, and concentrated to afford a 3:1 ratio of aldehyde to alcohol as a pale, yellow oil. The crude mixture is dissolved in MeOH (35 mL). Sodium borohydride (275 mg, 7.27 mmol) is added portionwise over 5 min. After 30 min, brine (50 mL) is added. The volatiles are removed under reduced pressure. The aqueous residue is extracted with CH_2Cl_2 (3 X 75 mL). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated to a pale yellow foam. Purification by flash column chromatography (1:1 hexanes:EtOAc, 50 g SiO_2) affords the title compound as a light yellow foam. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 2H), 4.23 (m, 1H), 3.94 (m, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 3.52-3.67 (m, 2H), 3.43 (m, 1H), 2.90-3.18 (m, 3H), 2.61 (s, 6H), 1.46 (s, 9H). LC-MS *m/z* ($M + Na^+$): 438.

Step 3. 3-Ethoxycarbonylmethoxymethyl-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)-piperazine-1-carboxylic acid *tert*-butyl ester



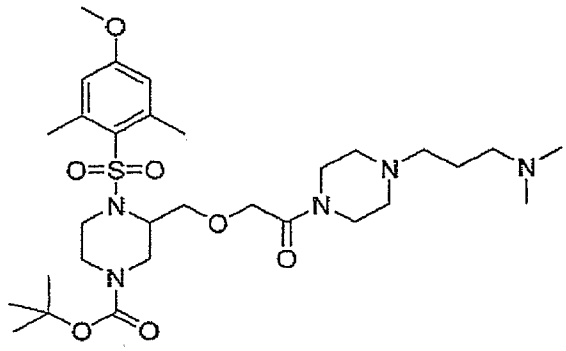
A 1.0 M solution of potassium *tert*-butoxide in THF (6.4 mL, 6.4 mmol) is added to a solution of 3-hydroxymethyl-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester (2.39 g, 5.77 mmol) and DMF (1.2 mL) at 0 °C under nitrogen. After 3 min, ethyl bromoacetate (830 μL, 7.5 mmol) is added. After 1 h, the cold bath is removed and the cloudy mixture is stirred at ambient temperature for 16 h. The reaction mixture is poured into 50% sat. aqueous NH_4Cl (150 mL). The solution is extracted with EtOAc (2 x 150 mL). The combined organic layers are washed with 50% sat. aqueous NH_4Cl (150 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (2:1 hexanes:EtOAc to 1.5:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, 100 g SiO_2) affords the title compound as a light yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.63 (s, 2H), 4.24 (m, 1H), 4.19 (q, 2H), 3.96-4.01 (m, 2H), 3.87 (m, 1H), 3.82 (s, 3H), 3.58-3.75 (m, 2H), 3.41 (m, 1H), 3.01-3.14 (m, 2H), 2.61 (s, 6H), 1.45 (s, 9H). LC-MS *m/z* ($M + Na^+$): 523.

Step 4. 3-Carboxymethoxymethyl-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester



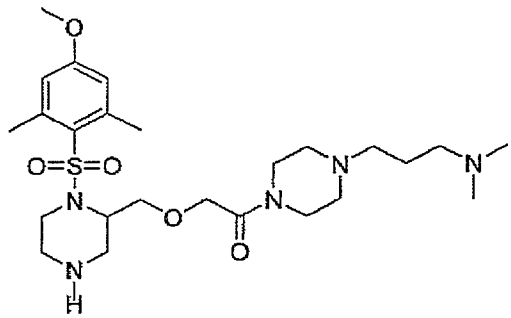
The title compound as a white foam is prepared as indicated above. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.63 (s, 2H), 3.90-4.26 (m, 5H), 3.83 (s, 3H), 3.61-3.82 (m, 3H), 2.94-3.22 (m, 3H), 2.62 (s, 6H), 1.44 (s, 9H). LC-MS *m/z* ($M + Na^+$): 496.

Step 5. 3-{2-[4-(3-Dimethylaminopropyl)piperazin-1-yl]-2-oxoethoxymethyl}-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester



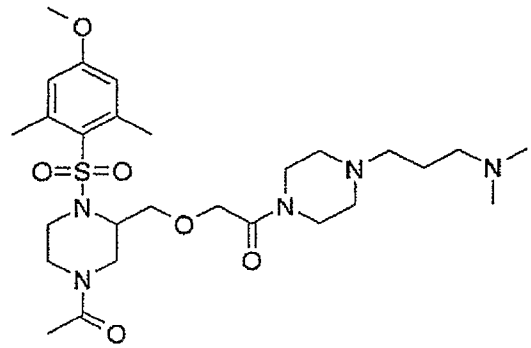
The title compound as a light yellow oil is prepared as indicated above. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 2H), 4.19 (d, 1H), 4.11 (d, 1H), 4.10 (d, 1H), 3.86 (m, 1H), 3.81 (s, 3H), 3.30-3.68 (m, 8H), 2.95-3.10 (m, 3H), 2.55-2.63 (m, 2H), 2.59 (s, 6H), 2.32-2.46 (m, 4H), 2.29 (dd, 2H), 2.22 (s, 6H), 1.65 (quintet, 2H), 1.44 (s, 9H). LC-MS *m/z* (M^+): 626.

Step 6. 1-[4-(3-Dimethylaminopropyl)piperazin-1-yl]-2-[1-(4-methoxy-2,6-dimethylbenzene-sulfonyl)piperazin-2-ylmethoxy]ethanone



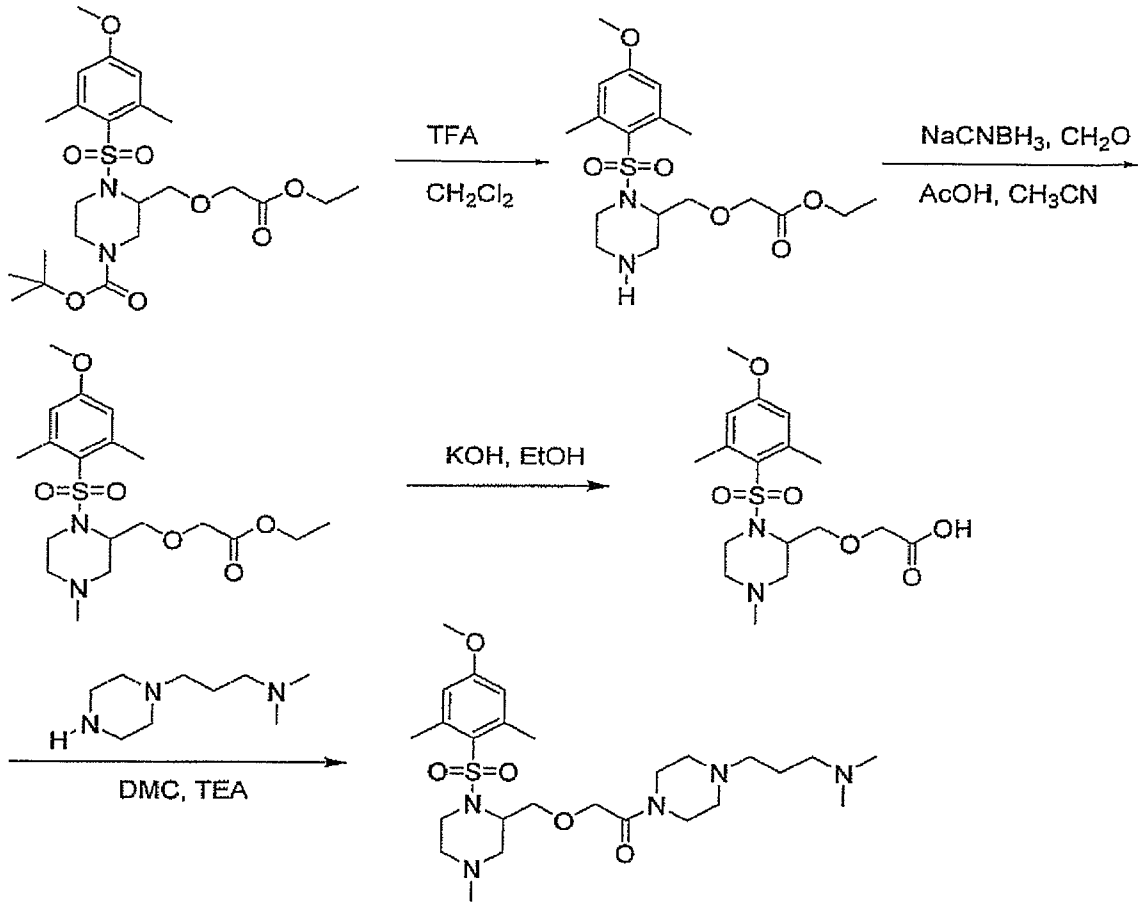
TFA (0.5 mL) is added in one portion to a solution of 3-{2-[4-(3-dimethylaminopropyl)piperazin-1-yl]-2-oxoethoxymethyl}-4-(4-methoxy-2,6-dimethyl-benzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester (69 mg, 110 μmol) and CH_2Cl_2 (0.5 mL). After 1.5 h, the volatiles are removed under reduced pressure. The residue is dissolved in 1 M aqueous NaOH (10 mL) and then extracted with EtOAc (2 x 25 mL). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.63 (s, 2H), 4.04-4.19 (m, 3H), 3.79-3.86 (m, 1H), 3.82 (s, 3H), 3.72 (dd, 1H), 3.56-3.63 (m, 2H), 3.38-3.44 (m, 2H), 3.27 (d, 1H), 3.08-3.19 (d, 2H), 2.85-2.95 (m, 2H), 2.67 (dd, 1H), 2.61 (s, 6H), 2.30-2.45 (m, 8H), 2.25 (s, 6H), 1.67 (quintet, 2H). LC-MS *m/z* (M^+): 526.

Step 7. 2-[4-Acetyl-1-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazin-2-ylmethoxy]-1-[4-(3-dimethylaminopropyl)pipazin-1-yl]ethanone

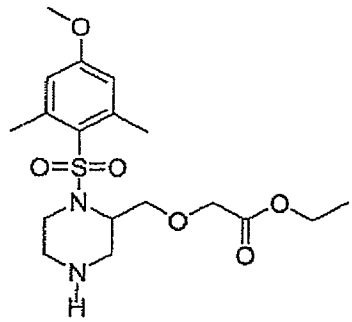


Ac_2O (10 μL, 100 μmol) is added to a solution of 1-[4-(3-dimethylamino-propyl)piperazin-1-yl]-2-[1-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazin-2-ylmethoxy]ethanone (40 mg, 76 μmol), pyridine (0.4 mL), and CH_2Cl_2 (0.4 mL). After 2 h, the volatiles are removed under reduced pressure. The residue is dissolved in 1 M aqueous NaOH (3 mL) and then extracted with EtOAc (3 mL). The organics are loaded onto two 0.5 g SCX columns. Each column is washed with MeOH (2 x 3 mL). Each column is then eluded with 5:5:2 EtOAc:MeOH:TEA (3 mL). Concentration of the organics under reduced pressure affords the title compound as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.62 (s, 1.3H), 6.60 (s, 0.7H), 4.03-4.15 (m, 3H), 4.13 (s, 1H), 4.10 (s, 2H), 3.96 (m, 1H), 3.72-3.84 (m, 1H), 3.80 (s, 3H), 3.10-3.70 (m, 8H), 2.88-3.05 (m, 1H), 2.58 (s, 6H), 2.25-2.43 (m, 8H), 2.21 (s, 6H), 2.12 (s, 2H), 2.06 (s, 1H), 1.64 (quintet, 2H). LC-MS *m/z* (M^+): 568.

B. 1-[4-(3-DIMETHYLAMINOPROPYL)PIPERAZIN-1-YL]-2-[1-(4-METHOXY-2,6-DIMETHYLBENZENE-SULFONYL)-4-METHYLPIPERAZIN-2-YLMETHOXY]ETHANONE

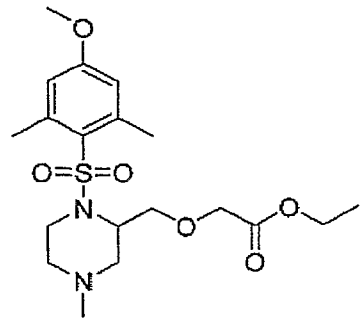


Step 1. [1-(4-Methoxy-2,6-dimethylbenzenesulfonyl)piperazin-2-ylmethoxy]acetic acid ethyl ester



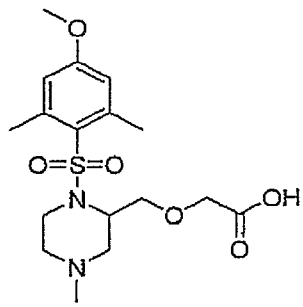
TFA (20 mL) is added in one portion to a solution of 3-ethoxycarbonyl-methoxymethyl-4-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazine-1-carboxylic acid *tert*-butyl ester (1.93 g, 3.86 mmol) and CH_2Cl_2 (20 mL). After 1.5 h, the volatiles are removed under reduced pressure. The residue is dissolved in 1 M aqueous NaOH (75 mL) and then extracted with EtOAc (2 x 200 mL). The combined organic layers are dried over Na_2SO_4, filtered, and concentrated to afford the title compound as a yellow-brown oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.64 (s, 2H), 4.04-4.26 (m, 5H), 3.72-3.88 (m, 2H), 3.82 (s, 3H), 3.14-3.38 (m, 3H), 2.91-3.04 (m, 2H), 2.72 (m, 1H), 2.62 (s, 6H), 1.23-1.32 (m, 2H). LC-MS *m/z* ($M + H^+$): 401.

Step 2. [1-(4-Methoxy-2,6-dimethylbenzenesulfonyl)-4-methylpiperazin-2-ylmethoxy]acetic acid ethyl ester



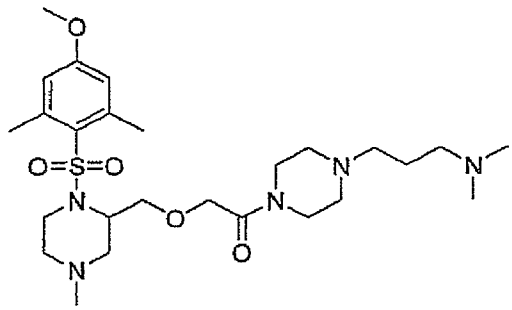
Sodium cyanoborohydride (1.1 g, 18 mmol) is added to a solution of [1-(4-methoxy-2,6-dimethylbenzenesulfonyl)piperazin-2-ylmethoxy]acetic acid ethyl ester (1.45 g, 3.62 mmol) and acetonitrile (40 mL) cooled in a water bath. 37% Aqueous formaldehyde (10 mL) is added in one portion. After 5 min, glacial acetic acid (1.8 mL) is added in three portions over 1.5 h. After 4 h, 0.1 M aqueous NaOH (15 mL) is added and the solution is stirred for 15 min. The reaction mixture is poured into CH_2Cl_2 (150 mL) and 1 M aqueous NaOH (15 mL). The layers are separated and the aqueous layer is extracted with CH_2Cl_2 (50 mL). The combined organic layers are washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (19:1 CH_2Cl_2:MeOH to 1% NH_4OH in 19:1 CH_2Cl_2:MeOH, 30 g SiO_2) affords the title compound as a pale orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.63 (s, 2H), 4.38 (s, 2H), 4.18 (q, 2H), 3.85-4.08 (m, 3H), 3.82 (s, 3H), 3.72 (m, 1H), 2.90-3.52 (m, 5H), 2.61 (s, 6H), 2.32 (bs, 3H), 1.28 (t, 3H). LC-MS *m/z* (M^+): 415.

Step 3. [1-(4-Methoxy-2,6-dimethylbenzenesulfonyl)-4-methylpiperazin-2-ylmethoxy]acetic acid



The title compound (as a yellow oil) is prepared as indicated above. ^{1}H-NMR (400 MHz, CD_3OD) δ: 6.74 (s, 2H), 3.88 (m, 1H), 3.82 (s, 3H), 3.75 (s, 2H), 3.60 (m, 1H), 3.38 (m, 1H), 3.08-3.27 (m, 3H), 2.68 (m, 1H), 2.59 (s, 6H), 2.23 (s, 3H), 2.13 (dd, 1H), 1.92 (ddd, 1H). LC-MS *m/z* ($M + H^+$): 387.

Step 4. 1-[4-(3-Dimethylaminopropyl)piperazin-1-yl]-2-[1-(4-methoxy-2,6-dimethylbenzene-sulfonyl)-4-methylpiperazin-2-ylmethoxy]ethanone



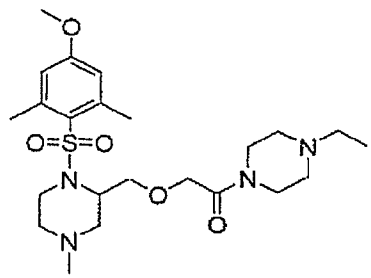
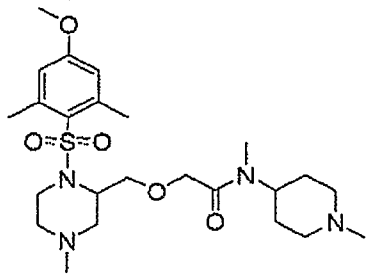
The title compound (as a pale yellow oil) is prepared as indicated above. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.60 (s, 2H), 4.07 (s, 2H), 3.84-3.96 (m, 2H), 3.80 (s, 3H), 3.66 (dd, 1H), 3.55-3.62 (m, 2H), 3.38-3.45 (m, 2H), 3.28 (m, 1H), 3.14 (ddd, 1H), 2.95 (d, 1H), 2.64 (m, 1H), 2.59 (s, 6H), 2.28-2.43 (m, 8H), 2.24 (s, 6H), 2.21 (s, 3H), 2.11 (dd, 1H), 1.92 (ddd, 1H), 1.67 (quintet, 2H). LC-MS *m/z* (M^+): 540.

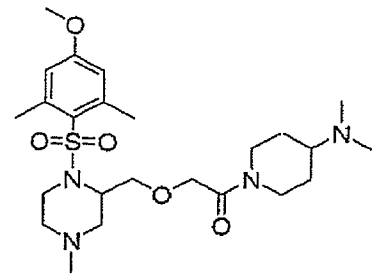
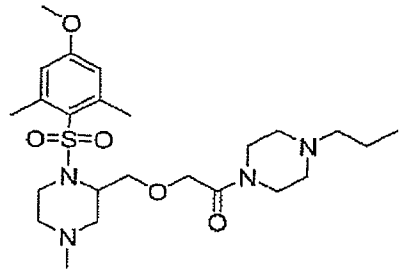
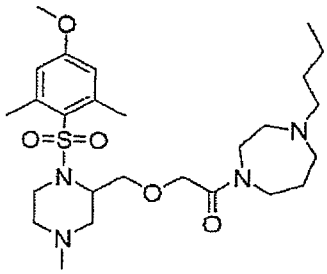
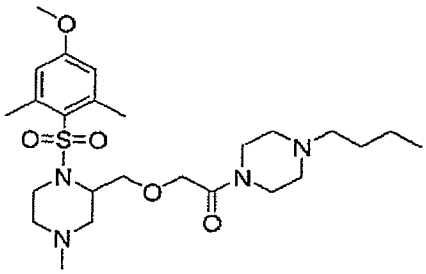
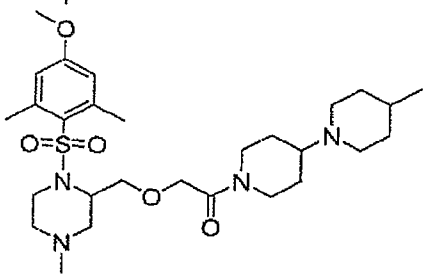
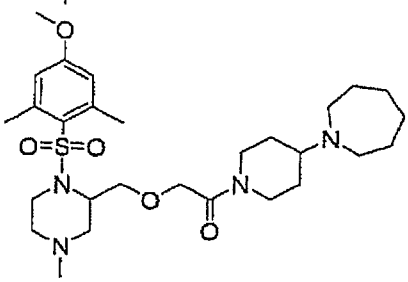
C. ADDITIONAL ARYL SULFONYL HETEROCYCLES

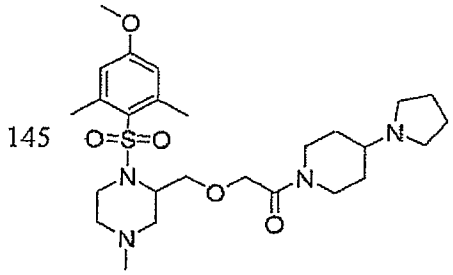
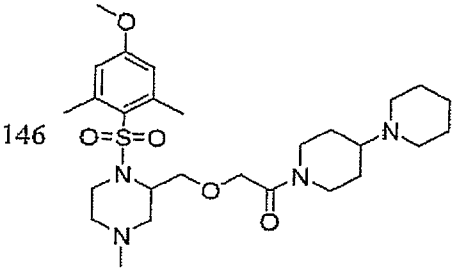
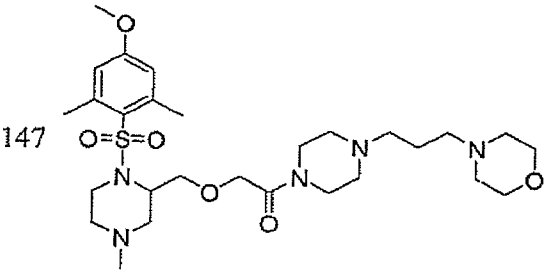
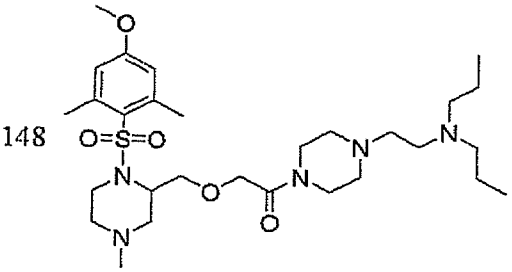
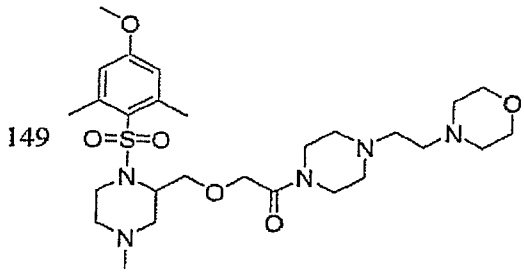
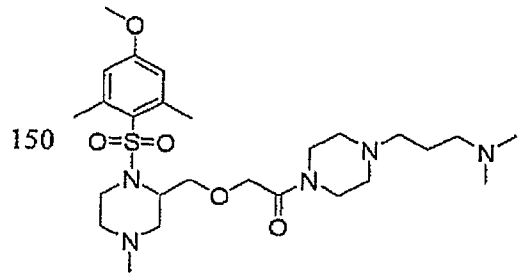
Using routine modifications of the methods illustrated above, the starting materials may be varied and additional steps employed to produce other aryl sulfonyl heterocycles. Compounds listed in Table III are prepared using such methods. All compounds in Table III exhibit an IC_{50} determined as described in Example 7 that is 5 micromolar or less. Mass spectroscopy (MS) data is provided as M+1, with retention times (Ret time) shown in minutes.

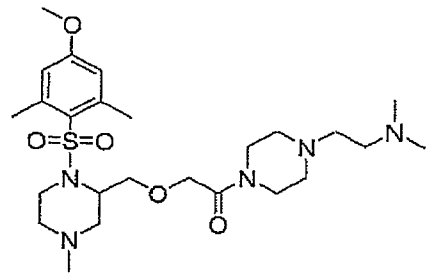
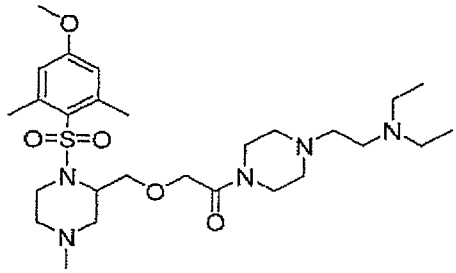
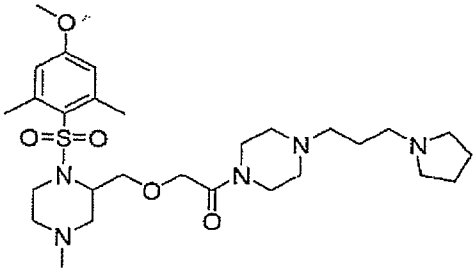
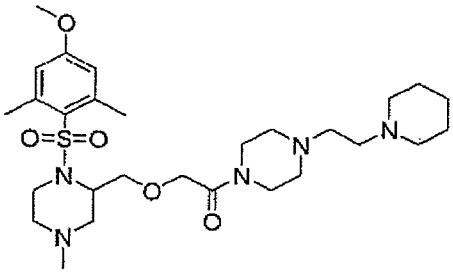
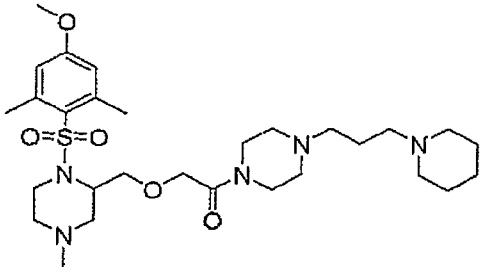
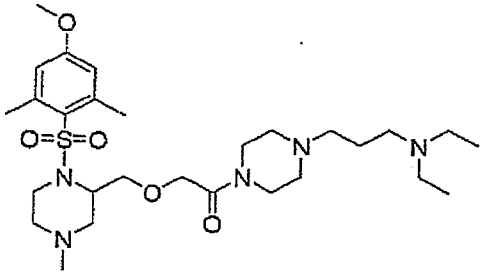
Table III

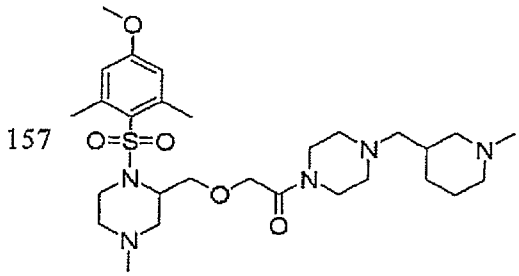
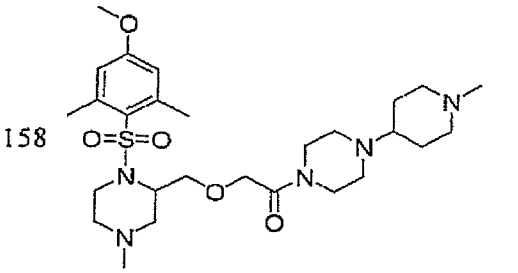
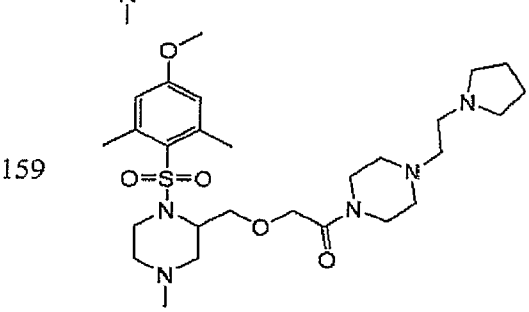
Representative Aryl Sulfonyl Heterocycles

Compound	Name	Ret Time	MS
137 	2-{[2-(4-ethylpiperazin-1-yl)-2-oxoethoxy]methyl}-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazine	1.08	483.18
138 	2-({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.1	497.20

Compound		Name	Ret Time	MS
139		1-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]-*N,N*-dimethylpiperidin-4-amine	1.08	497.20
140		1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-{[2-oxo-2-(4-propylpiperazin-1-yl)ethoxy]methyl}piperazine	1.1	497.21
141		1-butyl-4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]-1,4-diazepane	1.11	525.24
142		2-{[2-(4-butylpiperazin-1-yl)-2-oxoethoxy]methyl}-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazine	1.11	511.23
143		1'-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]-4-methyl-1,4'-bipiperidine	1.11	551.19
144		1-{1-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperidin-4-yl}azepane	1.11	551.18

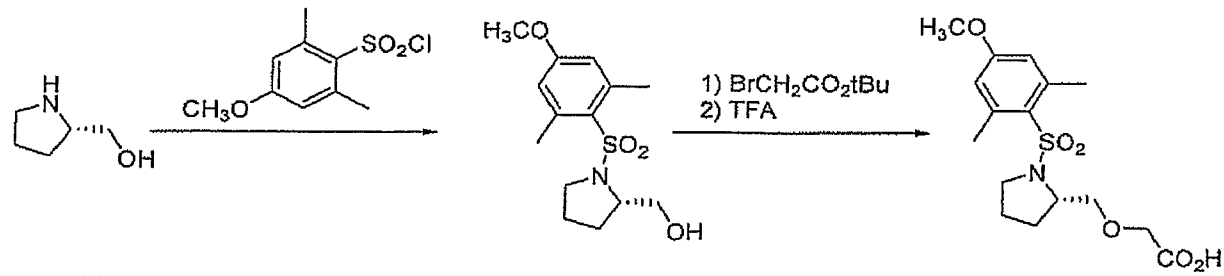
Compound	Name	Ret Time	MS
145 	1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-{[2-oxo-2-(4-pyrrolidin-1-ylpiperidin-1-yl)ethoxy]methyl}piperazine	1.09	523.15
146 	1'-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]-1,4'-bipiperidine	1.1	537.15
147 	4-(3-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}propyl)morpholine	1.07	582.16
148 	N-(2-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}ethyl)-N-propylpropan-1-amine	1.12	582.17
149 	4-(2-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}ethyl)morpholine	1.08	568.12
150 	3-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}-*N*,*N*-dimethylpropan-1-amine	1.06	540.14

	Compound	Name	Ret Time	MS
151		2-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylethanamine	1.08	526.13
152		*N,N*-diethyl-2-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}ethanamine	1.09	554.15
153		1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-({2-oxo-2-[4-(3-pyrrolidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)piperazine	1.06	566.14
154		1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-({2-oxo-2-[4-(2-piperidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)piperazine	1.1	566.13
155		1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-({2-oxo-2-[4-(3-piperidin-1-ylpropyl)piperazin-1-yl]ethoxy}methyl)piperazine	1.07	580.14
156		*N,N*-diethyl-3-{4-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methylpiperazin-2-yl}methoxy)acetyl]piperazin-1-yl}propan-1-amine	1.07	568.148

Compound	Name	Ret Time	MS
157 	1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-[(2-{4-[(1-methylpiperidin-3-yl)methyl]piperazin-1-yl}-2-oxoethoxy)methyl]piperazine	1.06	566.14
158 	1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-({2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethoxy}methyl)piperazine	1.05	552.12
159 	1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]-4-methyl-2-({2-oxo-2-[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]ethoxy}methyl)piperazine	1.09	552.12

EXAMPLE 3. SYNTHESIS OF REPRESENTATIVE ARYL SULFONYL HETEROCYCLES

A. SYNTHESIS OF (S)-2-((1-(4-METHOXY-2,6-DIMETHYLPHENYLSULFONYL)PYRROLIDIN-2-YL)METHOXY)ACETIC ACID



To a mixture of (S)-2-hydroxymethylpyrrolidine (1.21 g) and TEA (1.21g) in 50 mL CH_2Cl_2 is added 2,6-dimethyl-4-methoxysulfonyl chloride (2.35 g). The reaction mixture is stirred at room temperature for 12 hours. The reaction mixture is transferred to a separatory funnel and washed with 1.5 N HCl, and then with saturated $NaHCO_3$. The organic phase is dried over $MgSO_4$, filtered, and then concentrated to afford (S)-(1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methanol.

This sulfonamide is dissolved in 15 mL toluene. An aqueous 35% NaOH solution (30 mL) is added followed by tetrabutylammonium chloride (500 mg). Bromo-*tert*-butyl acetate (2.2 mL) is

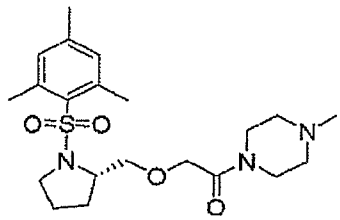
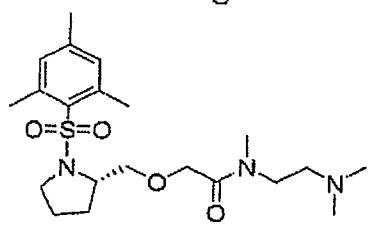
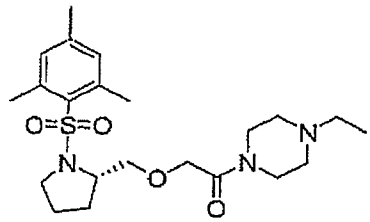
added and the two phase mixture is stirred vigorously at rt for 2 hours. The aqueous phase is removed and the organic phase is dried over Na_2SO_4, filtered, and concentrated. The product is purified by flash chromatography eluting with 85/15 hexanes/EtOAc to afford (S)-*tert*-butyl 2-((1-(4-methoxy-2,6-dimethylphenylsulfonyl)pyrrolidin-2-yl)methoxy)acetate.

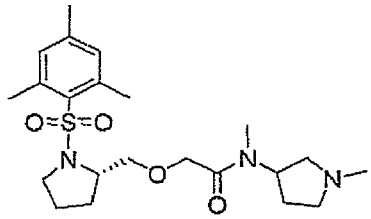
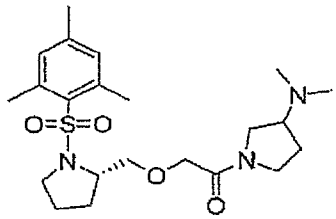
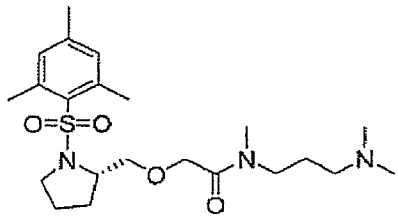
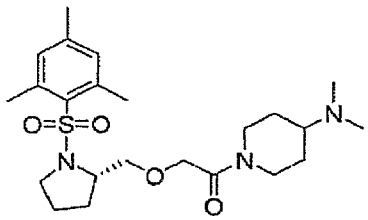
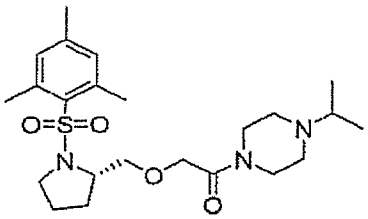
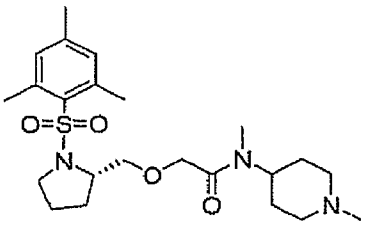
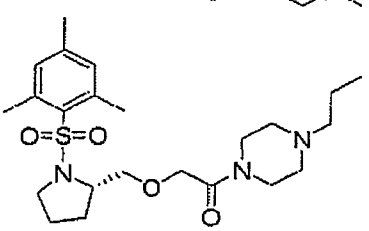
This ester is dissolved in 7 mL TFA and stirred 20 min at rt. The solvent is removed and the residue dissolved in EtOAc. The product is extracted into 1N NaOH. The aqueous phase is adjusted to pH~3 with 6N HCl and the product extracted into EtOAc. The organic phase is dried over Na_2SO_4, filtered and concentrated to afford the title compound. 400 MHz ^{1}H NMR ($CDCl_3$) δ; 11.72 (s, 1H), 6.60 (s, 2H), 4.06 (m, 1H), 3.86 (s, 2H), 3.79 (s, 3H), 3.40 (dd, 1H), 3.31 (d, 1H), 3.28 (m, 1H), 3.05 (m, 1H), 2.61 (s, 6H), 2.00 (m, 2H), 1.86 (m, 2H). LC-MS *m/z* (M+H): 358.01

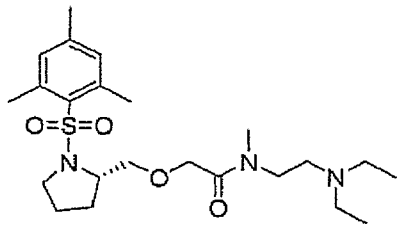
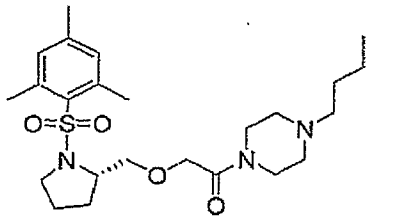
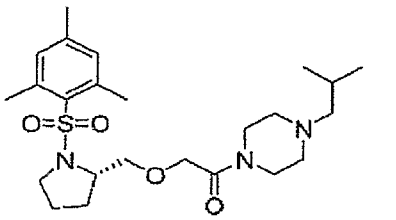
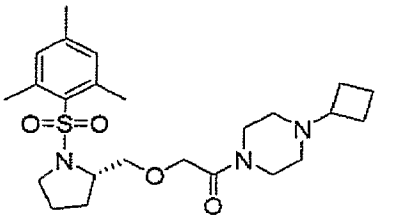
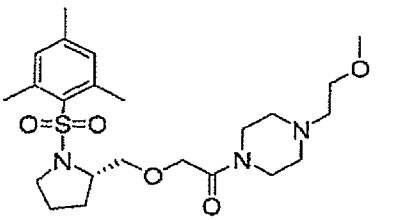
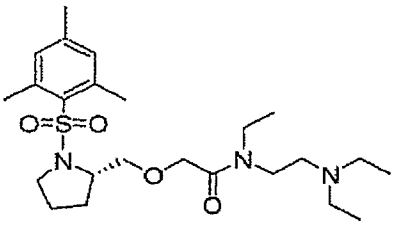
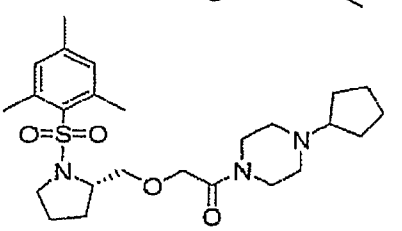
B. ADDITIONAL ARYL SULFONYL HETEROCYCLES

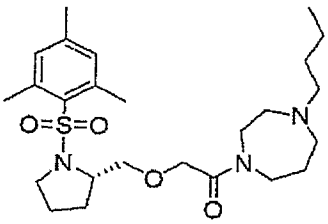
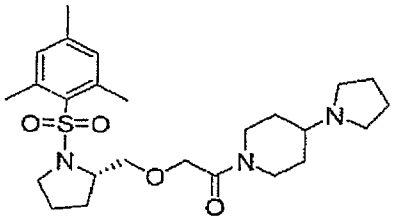
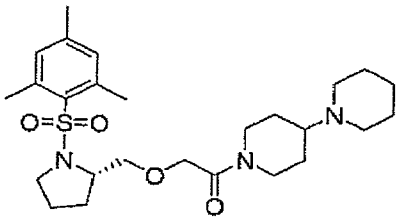
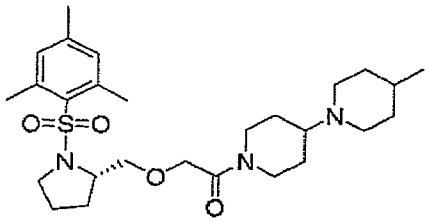
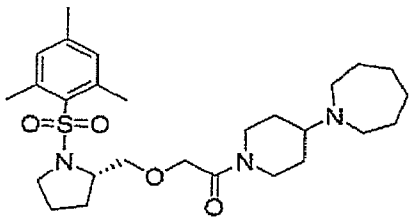
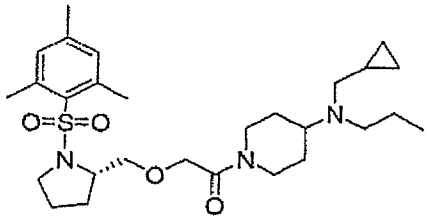
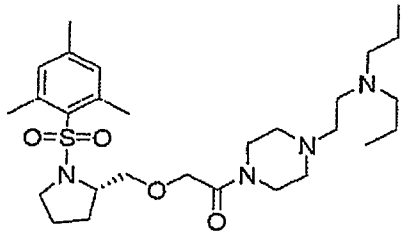
Using routine modifications of the methods illustrated above, the starting materials may be varied and additional steps employed to produce other aryl sulfonyl heterocycles. Compounds listed in Tables IV and V are prepared using such methods. All compounds in Tables IV and V exhibit an IC_{50} determined as described in Example 7 that is 5 micromolar or less. Mass spectroscopy (MS) data is provided as M+1, with retention times (Ret time) shown in minutes.

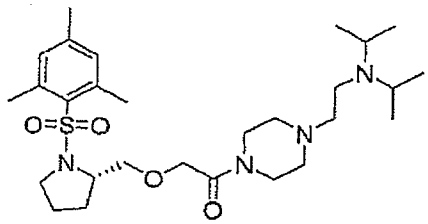
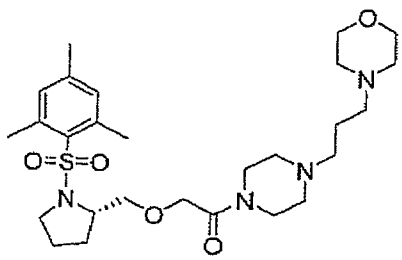
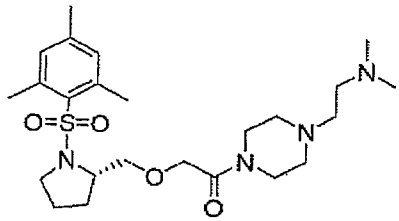
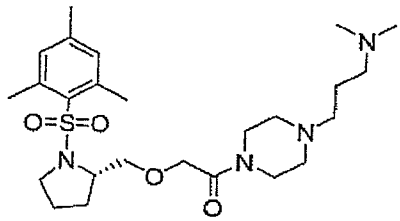
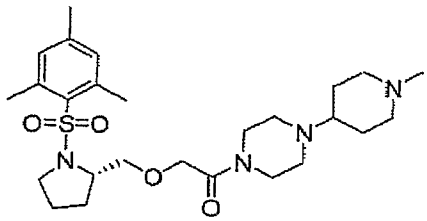
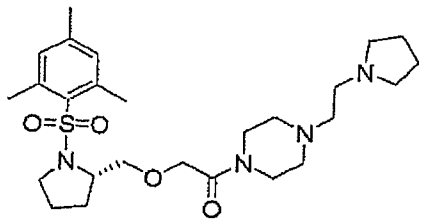
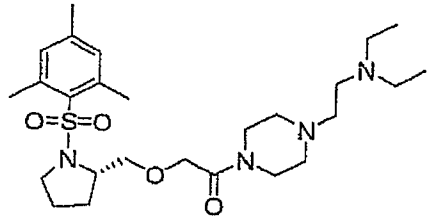
Table IV
Representative Aryl Sulfonyl Heterocycles

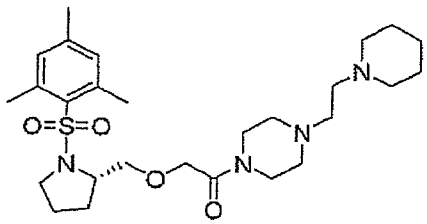
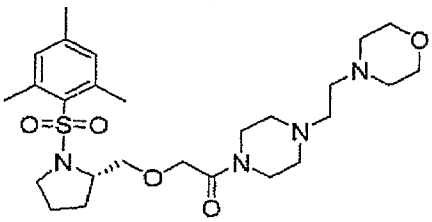
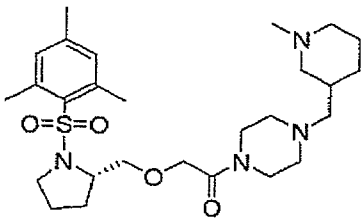
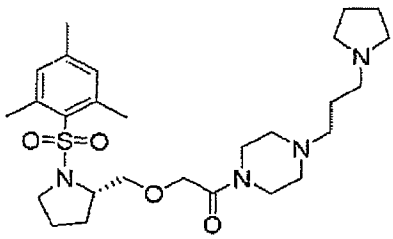
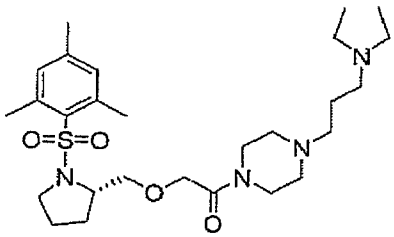
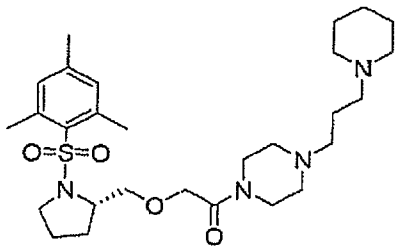
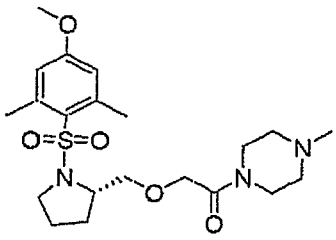
Compound	Name	Ret Time	MS
160 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-methylpiperazine	1.2	424.27
161 	N-[2-(dimethylamino)ethyl]-2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methylacetamide	1.2	426.28
162 	1-ethyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.2	438.29

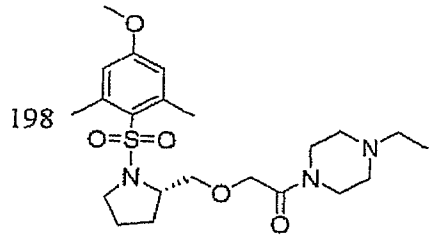
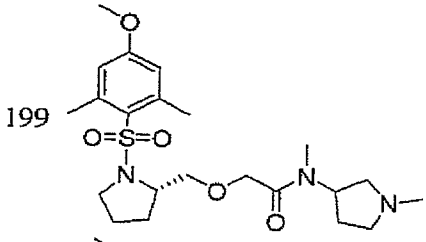
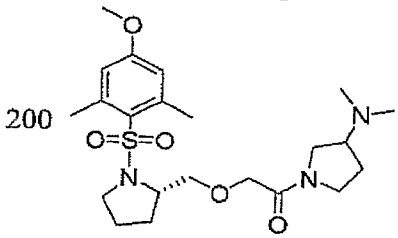
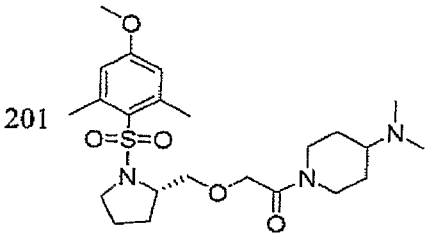
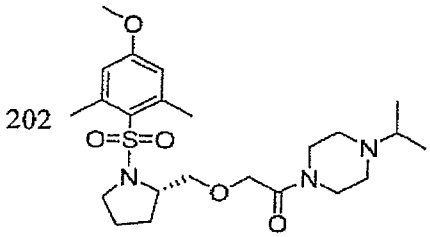
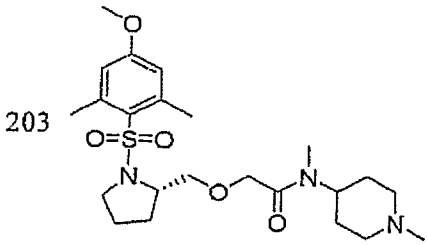
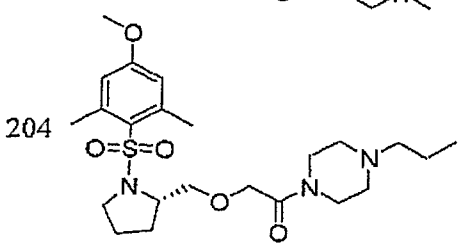
Compound	Name	Ret Time	MS
163 	2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methyl-N-(1-methylpyrrolidin-3-yl)acetamide	1.21	
164 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-*N,N*-dimethylpyrrolidin-3-amine	1.19	438.29
165 	N-[3-(dimethylamino)propyl]-2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methylacetamide	1.21	440.31
166 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-*N,N*-dimethylpiperidin-4-amine	1.2	452.31
167 	1-isopropyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.21	452.32
168 	2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.21	452.38
169 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-propylpiperazine	1.22	452.32

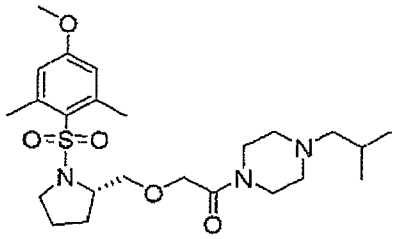
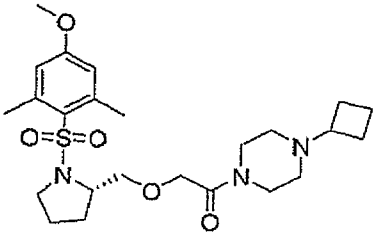
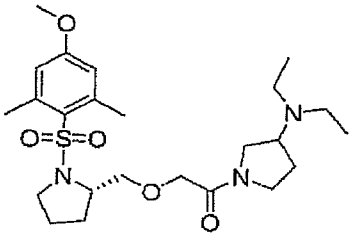
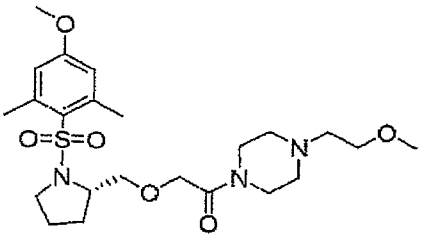
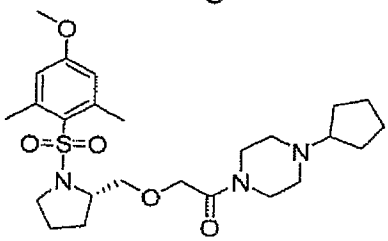
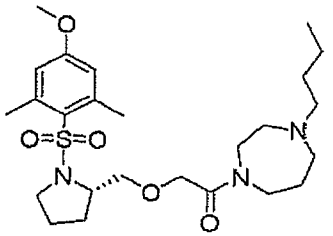
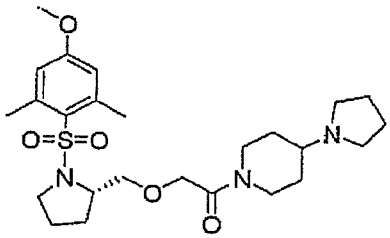
Compound	Name	Ret Time	MS
170 	N-[2-(diethylamino)ethyl]-2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methylacetamide	1.21	454.34
171 	1-butyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.23	466.34
172 	1-isobutyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.22	466.35
173 	1-cyclobutyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.22	464.34
174 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(2-methoxyethyl)piperazine	1.21	468.34
175 	N-[2-(diethylamino)ethyl]-N-ethyl-2-{[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetamide	1.23	468.36
176 	1-cyclopentyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.22	478.36

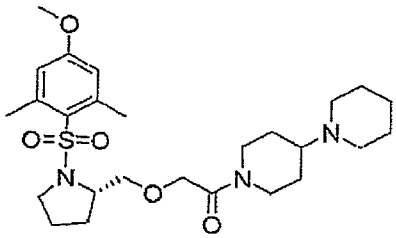
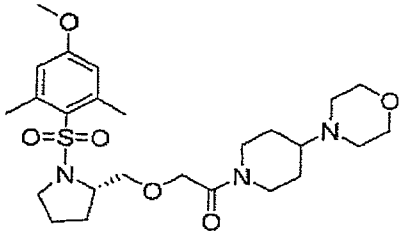
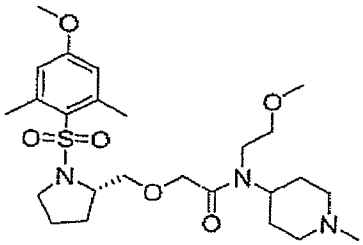
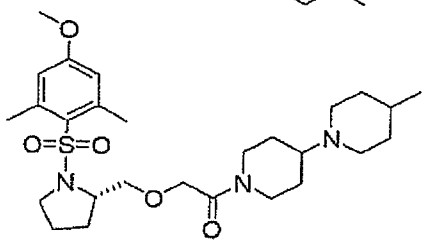
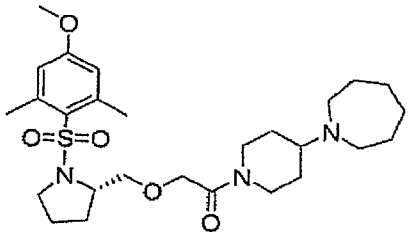
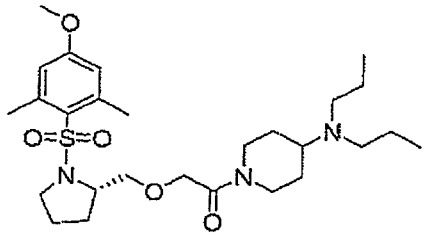
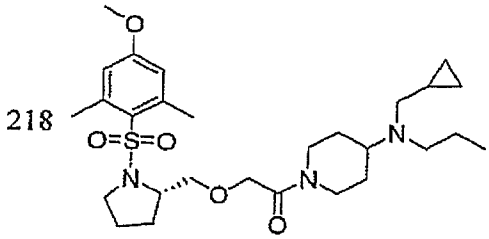
Compound	Name	Ret Time	MS
177 	1-butyl-4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-1,4-diazepane	1.22	480.37
178 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-pyrrolidin-1-ylpiperidine	1.2	478.36
179 	1'-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-1,4'-bipiperidine	1.21	492.38
180 	1'-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-methyl-1,4'-bipiperidine	1.22	506.40
181 	1-[1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperidin-4-yl]azepane	1.23	506.39
182 	N-(cyclopropylmethyl)-1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-N-propylpiperidin-4-amine	1.23	520.41
183 	N-{2-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]ethyl}-N-propylpropan-1-amine	1.22	537.45

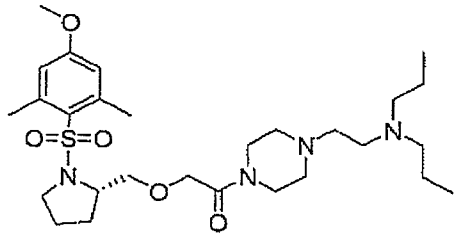
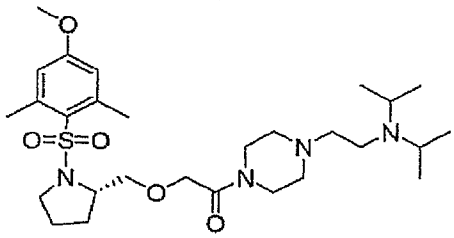
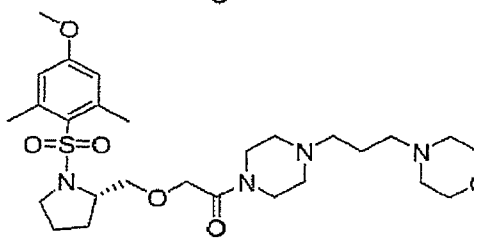
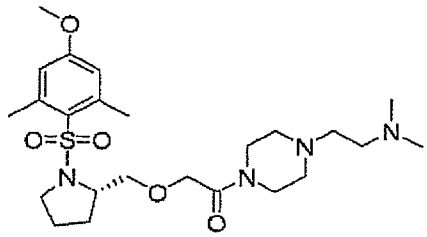
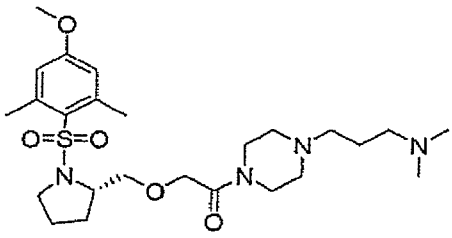
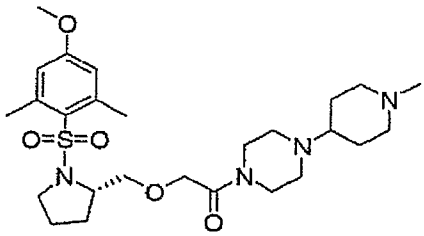
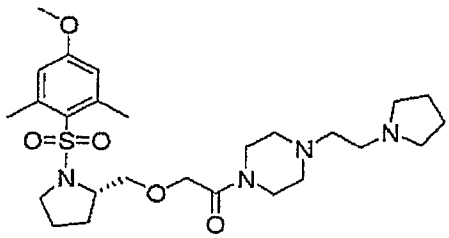
Compound	Name	Ret Time	MS
184 	N-isopropyl-N-{2-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]ethyl}propan-2-amine	1.21	537.45
185 	4-{3-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]propyl}morpholine	1.17	537.42
186 	2-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]-*N,N*-dimethylethanamine	1.2	481.37
187 	3-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]-*N,N*-dimethylpropan-1-amine	1.17	495.39
188 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(1-methylpiperidin-4-yl)piperazine	1.18	507.40
189 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(2-pyrrolidin-1-ylethyl)piperazine	1.2	507.40
190 	*N,N*-diethyl-2-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]ethanamine	1.2	509.42

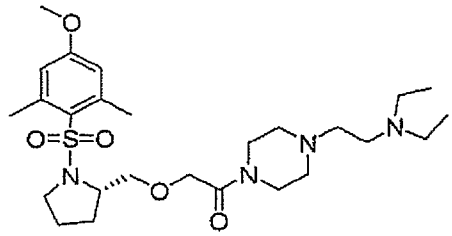
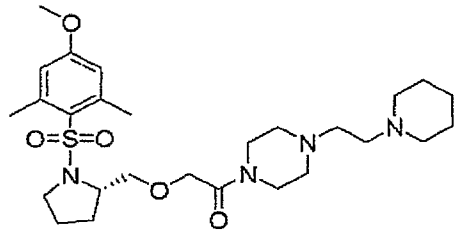
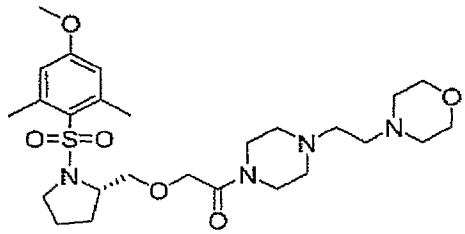
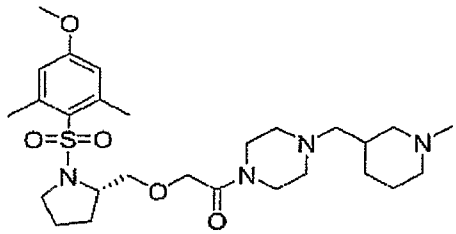
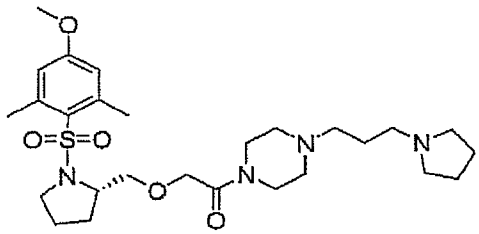
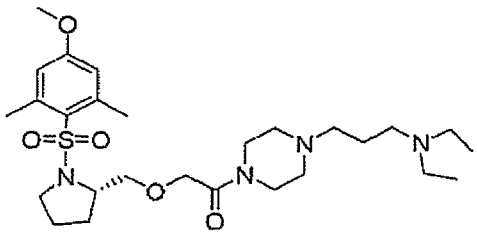
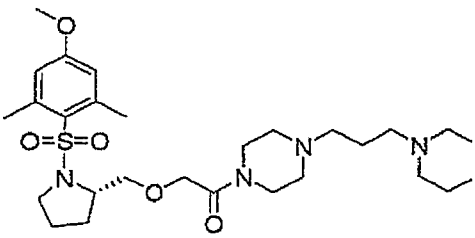
Compound	Name	Ret Time	MS
191 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(2-piperidin-1-ylethyl)piperazine	1.21	521.42
192 	4-{2-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]ethyl}morpholine	1.21	523.41
193 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-[(1-methylpiperidin-3-yl)methyl]piperazine	1.18	521.42
194 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(3-pyrrolidin-1-ylpropyl)piperazine	1.18	521.42
195 	*N,N*-diethyl-3-[4-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazin-1-yl]propan-1-amine	1.17	523.43
196 	1-({[(2S)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(3-piperidin-1-ylpropyl)piperazine	1.19	535.44
197 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-methylpiperazine	1.17	440.31

Compound	Name	Ret Time	MS
198 	1-ethyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine	1.17	454.33
199 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-methyl-N-(1-methylpyrrolidin-3-yl)acetamide	1.18	454.33
200 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-*N,N*-dimethylpyrrolidin-3-amine	1.16	454.33
201 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-*N,N*-dimethylpiperidin-4-amine	1.18	468.35
202 	1-isopropyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine	1.18	468.35
203 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.18	468.35
204 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-propylpiperazine	1.18	468.35

Compound	Name	Ret Time	MS
205 	1-isobutyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine	1.19	482.37
206 	1-cyclobutyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine	1.19	480.35
207 	*N,N*-diethyl-1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]pyrrolidin-3-amine	1.18	482.37
208 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(2-methoxyethyl)piperazine	1.17	484.34
209 	1-cyclopentyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine	1.2	494.37
210 	1-butyl-4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-1,4-diazepane	1.2	496.38
211 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-pyrrolidin-1-ylpiperidine	1.18	494.37

Compound	Name	Ret Time	MS
212 	1'-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-1,4'-bipiperidine	1.19	508.38
213 	4-{1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperidin-4-yl}morpholine	1.17	510.41
214 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-(2-methoxyethyl)-N-(1-methylpiperidin-4-yl)acetamide	1.21	512.38
215 	1'-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-methyl-1,4'-bipiperidine	1.2	522.39
216 	1-{1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperidin-4-yl}azepane	1.2	522.40
217 	1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-*N,N*-dipropylpiperidin-4-amine	1.21	524.42
218 	N-(cyclopropylmethyl)-1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-N-propylpiperidin-4-amine	1.21	536.41

	Compound	Name	Ret Time	MS
219		N-(2-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}ethyl)-N-propylpropan-1-amine	1.2	553.44
220		N-isopropyl-N-(2-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}ethyl)propan-2-amine	1.18	553.43
221		4-(3-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}propyl)morpholine	1.15	553.42
222		2-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylethanamine	1.17	497.37
223		3-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}-*N,N*-dimethylpropan-1-amine	1.15	511.38
224		1-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(1-methylpiperidin-4-yl)piperazine	1.15	523.40
225		1-[({1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(2-pyrrolidin-1-ylethyl)piperazine	1.17	523.40

Compound		Name	Ret Time	MS
226		*N,N*-diethyl-2-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}ethanamine	1.18	525.40
227		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(2-piperidin-1-ylethyl)piperazine	1.17	537.41
228		4-(2-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}ethyl)morpholine	1.17	539.40
229		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-[(1-methylpiperidin-3-yl)methyl]piperazine	1.15	537.41
230		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(3-pyrrolidin-1-ylpropyl)piperazine	1.15	537.40
231		*N,N*-diethyl-3-{4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazin-1-yl}propan-1-amine	1.15	539.43
232		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(3-piperidin-1-ylpropyl)piperazine	1.15	551.43

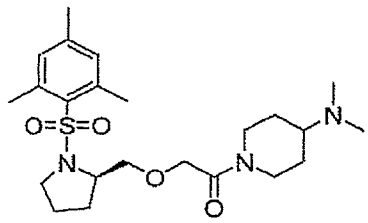
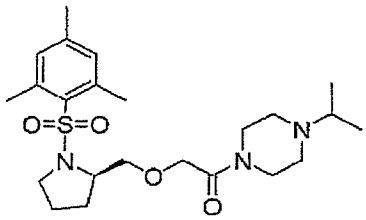
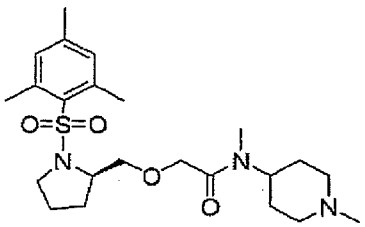
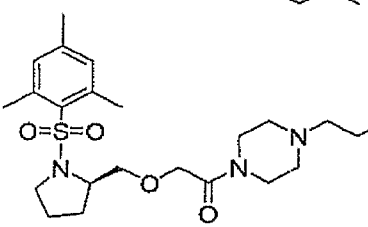
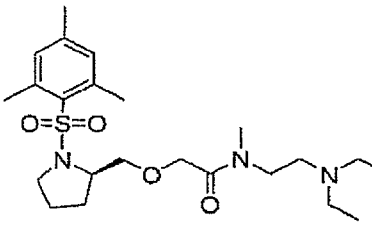
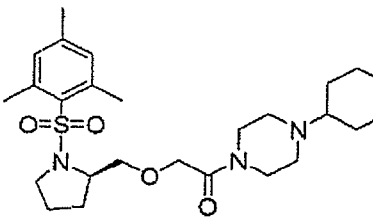
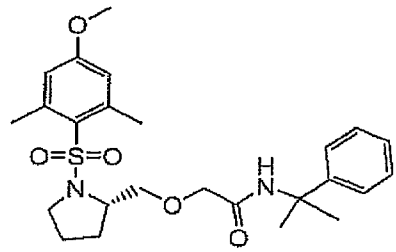
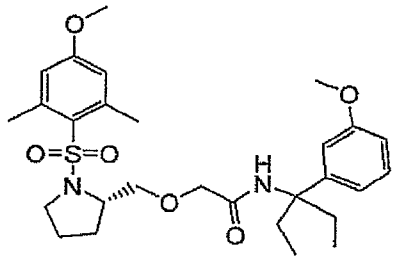
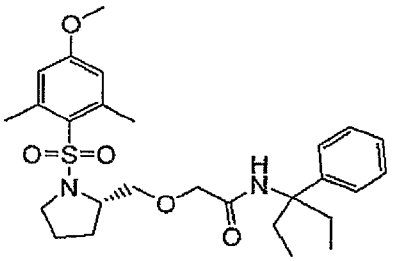
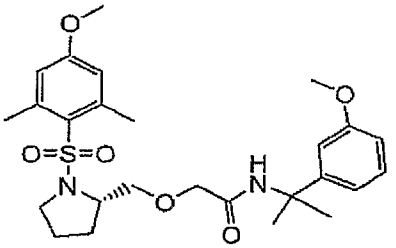
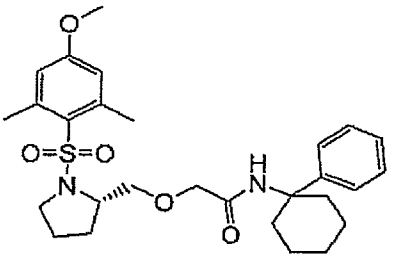
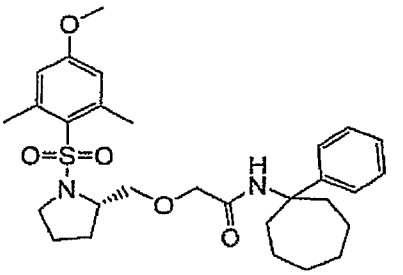
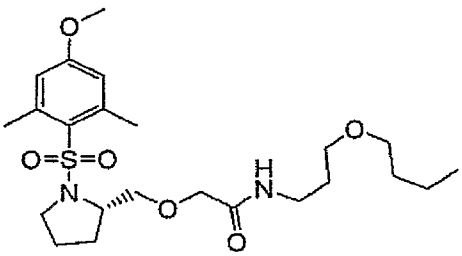
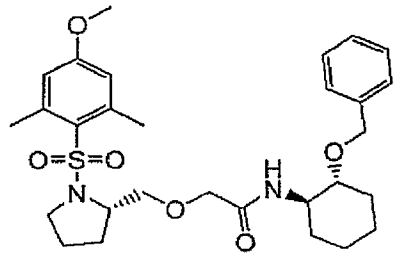
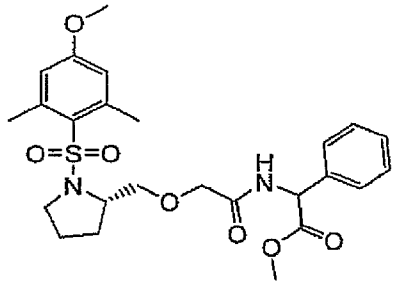
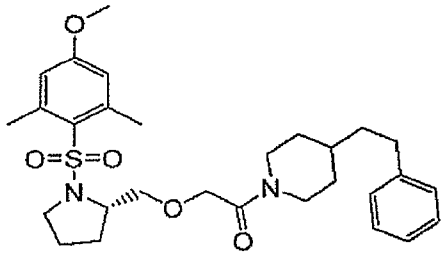
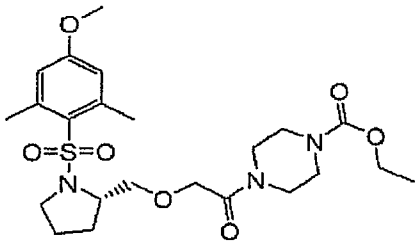
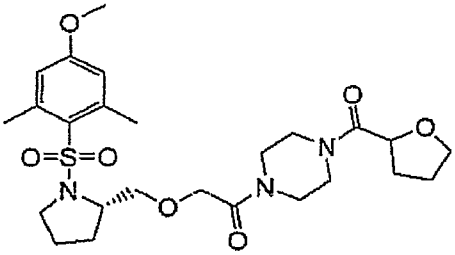
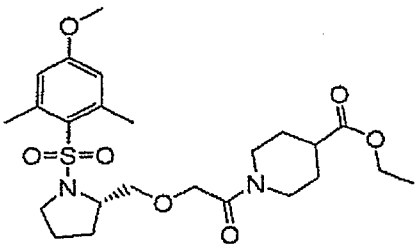
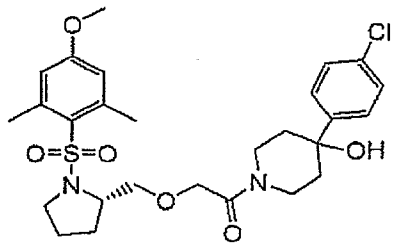
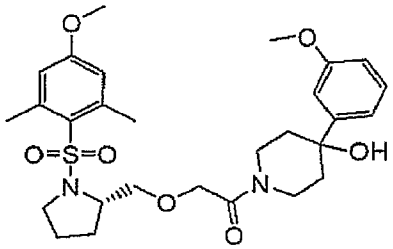
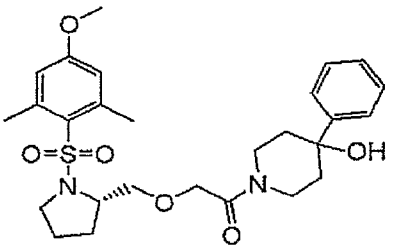
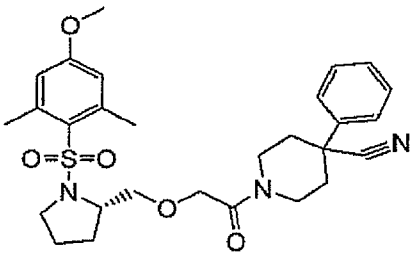
Compound		Name	Ret Time	MS
233		1-({[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-*N,N*-dimethylpiperidin-4-amine	1.21	452.29
234		1-isopropyl-4-({[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)piperazine	1.21	452.29
235		2-{[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methyl-N-(1-methylpiperidin-4-yl)acetamide	1.21	452.29
236		1-({[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-propylpiperazine	1.21	452.30
237		N-[2-(diethylamino)ethyl]-2-{[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}-N-methylacetamide	1.22	454.31
238		1-({[(2R)-1-(mesitylsulfonyl)pyrrolidin-2-yl]methoxy}acetyl)-4-(1-methylpiperidin-4-yl)piperazine	1.17	507.36

Table V
Representative Aryl Sulfonyl Heterocycles

Compound	Name	Ret Time	MS
239 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-(1-methyl-1-phenylethyl)acetamide	1.38	474.97
240 	N-[1-ethyl-1-(3-methoxyphenyl)propyl]-2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetamide	1.42	532.97
241 	N-(1-ethyl-1-phenylpropyl)-2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetamide	1.43	502.99
242 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-[1-(3-methoxyphenyl)-1-methylethyl]acetamide	1.39	504.96
243 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-(1-phenylcyclohexyl)acetamide	1.45	514.98
244 	2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)-N-(1-phenylcycloheptyl)acetamide	1.48	528.99

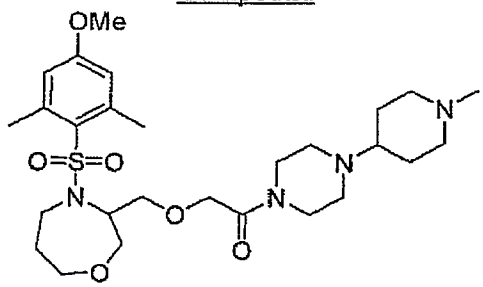
245		N-(3-butoxypropyl)-2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetamide	1.37	471.02
246		N-[(1R,2R)-2-(benzyloxy)cyclohexyl]-2-({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetamide	1.42	544.98
247		methyl {[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]amino}(phenyl)acetate	1.33	504.96
248		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(2-phenylethyl)piperidine	1.43	529.02
249		ethyl 4-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperazine-1-carboxylate	1.28	498.00
250		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(tetrahydrofuran-2-ylcarbonyl)piperazine	1.25	524.00
251		ethyl 1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperidine-4-carboxylate	1.3	497.00

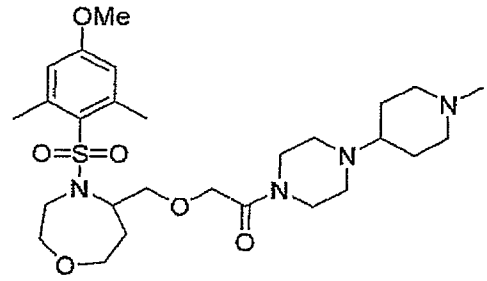
252		4-(4-chlorophenyl)-1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]piperidin-4-ol	1.35 550.95
253		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-(3-methoxyphenyl)piperidin-4-ol	1.32 546.99
254		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-phenylpiperidin-4-ol	1.31 517.00
255		1-[({(2S)-1-[(4-methoxy-2,6-dimethylphenyl)sulfonyl]pyrrolidin-2-yl}methoxy)acetyl]-4-phenylpiperidine-4-carbonitrile	1.34 526.00

EXAMPLE 4. ADDITIONAL REPRESENTATIVE COMPOUNDS

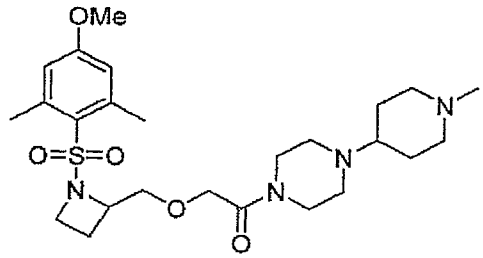
Using routine modifications, the starting materials may be varied and additional steps employed to produce other compounds provided herein. Compounds listed in Table VI are prepared using such methods.

Table VI

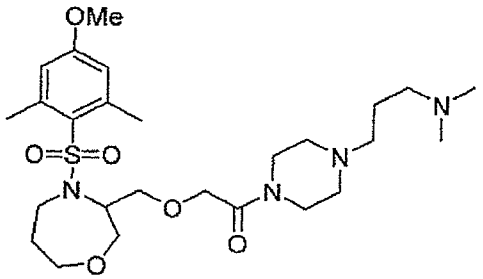
Compound		Name
208		2-[4-(4-Methoxy-2,6-dimethyl-benzenesulfonyl)-[1,4]oxazepan-3-ylmethoxy]-1-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-ethanone

209 

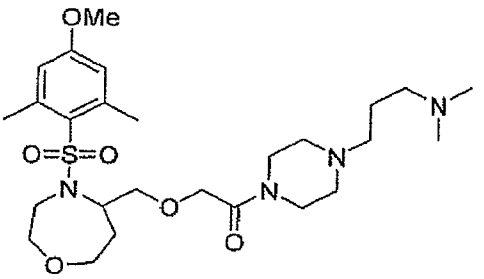
2-[4-(4-Methoxy-2,6-dimethyl-benzenesulfonyl)-[1,4]oxazepan-5-ylmethoxy]-1-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-ethanone

210 

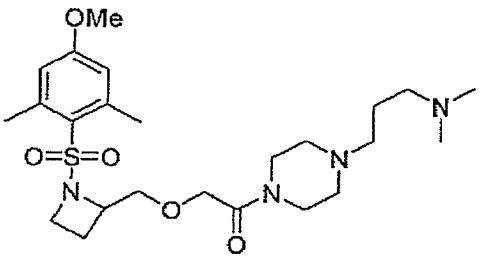
2-[1-(4-Methoxy-2,6-dimethyl-benzenesulfonyl)-azetidin-2-ylmethoxy]-1-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-ethanone

211 

1-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-2-[4-(4-methoxy-2,6-dimethyl-benzenesulfonyl)-[1,4]oxazepan-3-ylmethoxy]-ethanone

212 

1-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-2-[4-(4-methoxy-2,6-dimethyl-benzenesulfonyl)-[1,4]oxazepan-5-ylmethoxy]-ethanone

213 

1-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-2-[1-(4-methoxy-2,6-dimethyl-benzenesulfonyl)-azetidin-2-ylmethoxy]-ethanone

EXAMPLE 5. PREPARATION OF B_1-TRANSFECTED CELLS

This Example illustrates the preparation of B_1-transfected cells for use in B_1 binding and modulation assays (Examples 6 and 7).

Cynomolgus macaque lung total RNA is isolated as described by Chomzynski et al. (1987) *Anal. Biochem. 162*:156-159. A cDNA encoding B_1 is cloned from the total RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) with the following oligonucleotides:

Primer 1: GGCGCTAGCCACCATGGCATCCTGGCCCCCTC (SEQ ID NO:1)

Primer 2: AGCCGTCCCAGATCTGAAC (SEQ ID NO:2)

Primer 3: GATCTGGGACGGCTTGGATG (SEQ ID NO:3)

Primer 4: CGGAGCTCTTAATTCCGCCAGAAAAGTTGGA (SEQ ID NO:4)

Primer pairs 1 & 2 and 3 & 4 are used to generate overlapping cDNA fragments corresponding to the entire protein coding sequence of cynomolgus macaque B_1 cDNA are isolated and linked to form the full-length coding sequence (GenBank Accession Number AY788905). The construct is cloned into pcDNA 3.1 (Invitrogen, Carlsbad, CA) and transfected into Chinese hamster ovary (CHO) cells using Lipofectamine (Invitrogen), resulting in cynomolgus macaque B_1-expressing CHO cells. Alternatively, the construct is cloned into pBAKPAK9 (Clontech, Mountain View, CA) and transfected into Sf9 cells to generate clonal baculovirus stocks. Clonal cell lines stably expressing the cynomolgus macaque B_1 receptor are selected in G418. A single clonal line that exhibits high levels of receptor expression is chosen for use in binding and calcium mobilization assays (Examples 6 and 7). Clonal baculovirus stocks are used to infect Sf9 cells such that the infected cells express high levels of recombinant B_1 receptors. These cells are used in radioligand binding assays (Example 6).

EXAMPLE 6. B_1 RECEPTOR BINDING ASSAYS

This Example illustrates a representative B_1 receptor binding assay that may be used to determine the binding affinity of compounds for B_1.

A. [3H]-DESARG^{10}KALLIDIN BINDING TO INTACT IMR-90 CELLS OR CHO CELLS STABLY EXPRESSING RAT B_1

IMR-90 cells, which endogenously express human B_1, are seeded into 24 well plates at 65,000 cells per well, cultured overnight, and then treated for 3 h with 0.2 ng/mL interleukin-1 beta to induce B_1 expression (Menke, et al. (1994) *J. Biol. Chem.* 269:21583-86). CHO cells stably expressing rat B_1 are seeded into 24 well plates at 200,000 cells per well and cultured overnight. The cells are then washed 3 times with phosphate buffered saline (PBS). One hundred fifty microliters of binding buffer (50 mM Tris 7.4, 0.14 mg/mL, bacitracin, and 1 mg/mL BSA) is added to each well. Various concentrations of test compound are added to each well from DMSO solutions such the final DMSO concentration is 1% by volume; some wells receive DMSO only, and some wells receive DMSO plus 10 μM desArg^{10}Kallidin to define non-specific binding. All wells then receive 0.3 nM (final concentration) [3H]-desArg^{10}Kallidin. The plates are allowed to sit for 2 h at room temperature. Cells are then washed three times, and lysed with 400 μl Ultima Gold scintillation fluid (PerkinElmer; Boston, MA; 20 min incubation). The fluid is then transferred to counting vials counted in a Packard liquid scintillation counter (PerkinElmer). The number of counts present in the scintillation fluid is plotted as a function of antagonist compound concentration and fitted to a logistical equation using SigmaPlot (Systat Software, Point Richmond, CA) to determine each compound's IC_{50} and K_i (*e.g.*, as described by Szallasi, et al. (1993) *J. Pharmacol. Exp. Ther. 266*:678-83).

B. [3H]-DESARD[10]KALLIDIN BINDING TO MEMBRANE HOMOGENATES OF SF9 CELLS EXPRESSING CYNOMOLGUS MACAQUE B_1

Sf9 cells infected with a baculovirus carrying the coding sequence for cynomolgus macaque B_1 are harvested by centrifugation and frozen at -80 °C. Pellets are subsequently resuspended on ice in Tris buffered saline (TBS; 50 mM Tris (pH 7.4), 120 mM NaCl), and cells are homogenized using a polytron for 30 seconds. The crude membrane fraction is collected by centrifugation at 20,000 rpm. Membranes are washed two times with TBS and collected by centrifugation each time. Protein content of the membranes is determined after the last wash and the concentration is adjusted to 0.7 µg/uL with binding buffer (50 mM Tris 7.4, 0.14 mg/mL bacitracin, and 1.0 mg/mL BSA). To perform the binding assay, 150 microliters of membrane fraction is added to each well of a 96-well plate along with 50 µl [^{3}H]-desArg[10]Kallidin (0.3 nM final) and test compound in DMSO (final DMSO concentration = 1%). Some wells receive DMSO only, and some wells receive DMSO plus 10 µM desArg[10]Kallidin to define non-specific binding. The 96 well plates are allowed to sit for 2 h at room temperature. Membrane proteins are then harvested by filtration onto GF/C filtermats (PerkinElmer) pre-soaked for 1 hr in 0.5 % polyethylenimine. After filtration, filters are dried and then counted in a Beta plate counter. The number of counts present in the scintillation fluid is plotted as a function of antagonist compound concentration and fitted to a logistical equation using SigmaPlot (Systat Software, Point Richmond, CA) to determine each compound's IC_{50} and K_i (*e.g.*, as described by Szallasi, *et al.* (1993) *J. Pharmacol. Exp. Ther.* 266:678-83).

EXAMPLE 7. CALCIUM MOBILIZATION ASSAY

This Example illustrates representative calcium mobilization assays for use in evaluating test compounds for agonist and antagonist activity.

Cynomolgus macaque B_1-expressing CHO cells (Example 5) are plated in a 96 well plate. The cells are cultured for 1 day, after which culture media is emptied from the plate and replaced with 50 µl of KRH (Krebs-Ringer HEPES buffer: 25 mM HEPES, 5 mM KCl, 0.96 mM NaH_2PO4, 1 mM $MgSO_4$, 2 mM $CaCl_2$, 5 mM glucose, 1 mM probenecid, pH 7.4) supplemented with the calcium-sensitive fluorescent dye Fluo4-AM (5 µg/ml; Teflabs, Austin, TX). The cells are then incubated at 37 °C in an environment containing 5% CO_2. After the 1 hour incubation, the dye solution is removed from the plate, the plate is washed once with KRH, and 100 µL KRH is added.

DETERMINATION OF B_1 AGONIST ACTIVITY

100 µL KRH + 2% DMSO is added to each well of cells, such that the final volume in each well is 200 microliters and the final DMSO concentration is 1%. Various concentrations of the B_1 agonist desArg[10]Kallidin are added. Addition of desArg[10]Kallidin elicits a fluorescent response as consequence of increased intracellular calcium. This response is measured with a FLIPR instrument (Molecular Devices, Sunnyvale, CA) and determined to be desArg[10]Kallidin concentration dependent.

A plot of maximum fluorescent response as a function of desArg^{10}Kalligin is generated and an EC_{50} (concentration required to elicit a 50% of maximal response) for the response is determined using the equation:

$$y=a*(1/(1+(b/x)^c))$$

In this equation, y is the maximum fluorescence signal, x is the concentration of the B_1 agonist, a is the E_{max}, b corresponds to the EC_{50} value and c is the Hill coefficient.

By replacing the desArg^{10}Kallidin with a test compound, this assay is also used to assess B_1 agonist activity of the test compound.

DETERMINATION OF ANTAGONIST ACTIVITY

Various concentrations of test compounds are added to the cell plate prepared as described above in 100 µL KRH + 2% DMSO, such that the final volume in each well is 200 microliters and the final DMSO concentration is 1%. The EC_{50} concentration of desArg^{10}Kallidin is then added to each well of plates containing test compound to determine the extent to which each test compound inhibits an agonist-induced B_1 response. The maximum fluorescent response is plotted as a function of test compound concentration in order to determine the IC_{50} (concentration required to inhibit 50% of the effect of agonist) for each compound at B_1. Antagonists of B_1 decrease this response by at least about 20%, preferably by at least about 50%, and most preferably by at least 80%, as compared to matched control (*i.e.*, cells treated with desArg^{10}Kallidin at the EC_{50} concentration in the absence of test compound), at a concentration of 10 micromolar or less, preferably 1 micromolar or less.

Alternatively, the data is analyzed as follows. First, the average maximum relative fluorescent unit (RFU) response from negative control wells (no agonist) is subtracted from the maximum response detected for each of the other experimental wells. Second, average maximum RFU response is calculated for the positive control wells (agonist wells). Then, percent inhibition for each compound tested is calculated using the equation:

$$\text{Percent Inhibition} = 100 - 100 \times \left[\frac{\text{Peak Signal in Test Wells}}{\text{Peak signal in Agonist Wells}} \right]$$

The % inhibition data is plotted as a function of test compound concentration and test compound IC_{50} is determined using a linear regression in which x is ln(concentration of test compound) and y is ln(percent inhibition/(100 - percent inhibition). Data with a percent inhibition that is greater than 90% or less than 15% are rejected and are not used in the regression. The IC_{50} is $e^{(-\text{intercept/slope})}$.

EXAMPLE 8. MDCK CYTOTOXICITY ASSAY

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 µL of test compound is added to each well of a clear bottom 96-well plate (Packard,

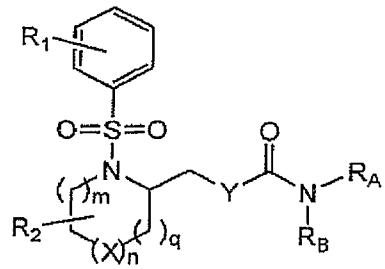
Meriden, CT) to give final concentration of compound in the assay of 10 μM, 100 μM or 200 μM. Solvent without test compound is added to control wells.

MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/mL with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μL of diluted cells is added to each well, except for five standard curve control wells that contain 100 μL of warm medium without cells. The plate is then incubated at 37°C under 95% O_2, 5% CO_2 for 2 hours with constant shaking. After incubation, 50 μL of mammalian cell lysis solution (from the Packard (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit) is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 min.

Compounds causing toxicity will decrease ATP production, relative to untreated cells. The ATP-LITE-M Luminescent ATP detection kit is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM, and 12.5 nM. PACKARD substrate solution (50 μL) is added to all wells, which are then covered, and the plates are shaken at approximately 700 rpm on a suitable shaker for 2 min. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 min. Luminescence is then measured at 22°C using a luminescence counter (*e.g.*, PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μM of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μM concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated cells.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0 or 1;

if n is 0, then m is 1 and q is 0 or 1;

if n is 1, then either (i) m is 1 and q is 1 or 2 or (i) q is 1 and m is 1 or 2;

X is NR_3, O, S, SO or SO_2;

Y is $-O-CH_2-$, $-N(R_{10})-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-$ or $-O-CH_2-CH_2-$;

R_1 represents from 0 to 5 substituents independently chosen from:

(i) halogen, hydroxy, cyano, amino, nitro, aminocarbonyl, aminosulfonyl and –COOH;

(ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkylsulfonylC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminosulfonylC_0-C_4alkyl, mono- or di-(C_1-C_6alkyl)aminocarbonylC_0-C_4alkyl, and (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl; each of which is substituted with from 0 to 6 substituents independently chosen from halogen, hydroxy, cyano and amino; and

(iii) groups that are taken together to form a fused carbocyclic ring that is substituted with from 0 to 4 substituents independently chosen from halogen, hydroxy, cyano, amino, nitro, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, and mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl;

R_2 represents from 0 to 4 substituents independently chosen from oxo, hydroxy and C_1-C_8alkyl;

R_3 is hydrogen, C_1-C_8alkyl or C_1-C_8alkanoyl;

R_{10} is hydrogen or C_1-C_4alkyl;

R_A is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, or mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl; and

R_B is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, or (4- to 7-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 6 substituents independently chosen from:

(i) amino, halogen, hydroxy, cyano and oxo; and

(ii) C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, phenylC_0-C_4alkyl and (5- or 6-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 4 substituents

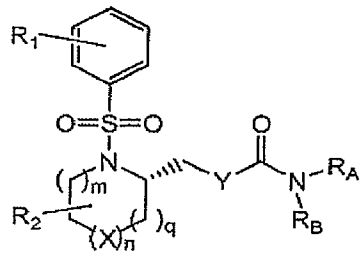
independently chosen from amino, cyano, halogen, hydroxy, C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, mono- or di-(C_1-C_6alkyl)amino, phenylC_0-C_4alkyl and phenylC_0-C_4alkoxy;

or R_A and R_B are taken together to form a 4- to 7-membered heterocycloalkyl that is substituted with from 0 to 4 substituents independently chosen from:

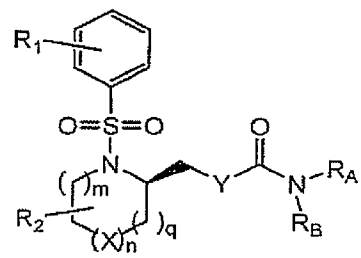
(i) hydroxy, oxo, cyano and amino; and

(ii) C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl.

2. A compound, salt or hydrate according to claim 1, wherein the compound satisfies the formula:



or



.

3. A compound, salt or hydrate according to claim 1 or claim 2, wherein n is 0.

4. A compound, salt or hydrate according to claim 1 or claim 2, wherein n is 1.

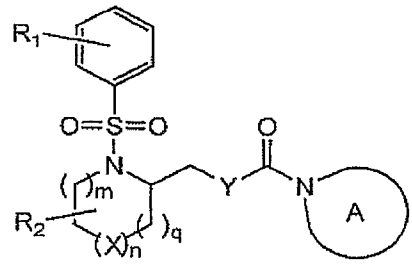
5. A compound, salt or hydrate according to any one of claims 1-4, wherein R_1 represents from 1 to 3 substituents independently chosen from halogen, hydroxy, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy and C_1-C_6haloalkoxy.

6. A compound, salt or hydrate according to any one of claims 1-5, wherein R_2 represents from 0 to 4 substituents independently chosen from C_1-C_2alkyl.

7. A compound, salt or hydrate according to claim 6, wherein R_2 represents gem-dimethyl.

8. A compound, salt or hydrate according to any one of claims 1-7, wherein Y is $-O-CH_2-$.

9. A compound, salt or hydrate according to any one of claims 1-8, wherein the compound satisfies the formula:

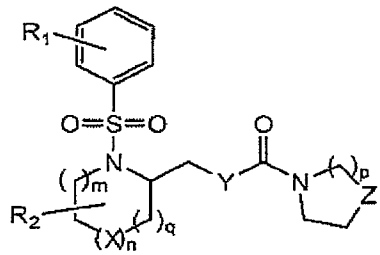


wherein  represents a 4- to 7-membered, N-linked heterocycloalkyl that is substituted with from 0 to 4 substituents independently chosen from:

(i) hydroxy, oxo, cyano and amino; and

(ii) C_1-C_6alkyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl; each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_6alkyl, C_1-C_6alkoxy, (C_3-C_{10}carbocycle)C_0-C_4alkyl and (4- to 10-membered heterocycle)C_0-C_4alkyl.

10. A compound, salt or hydrate according to claim 9, wherein the compound satisfies the formula:



wherein:

p is 0, 1, 2 or 3;

Z is CR_7R_8 or NR_9;

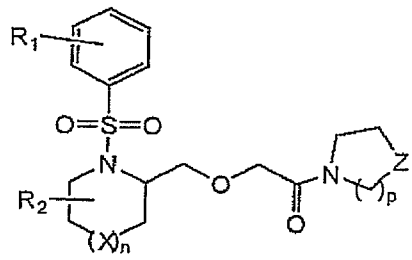
R_7 and R_8 are independently chosen from:

(i) hydrogen, hydroxy and cyano; and

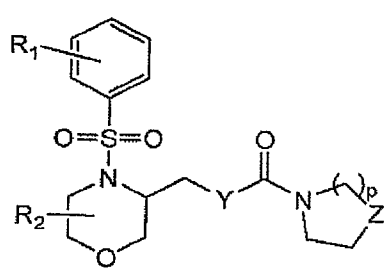
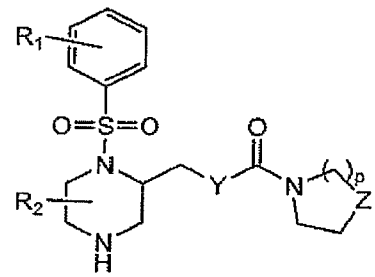
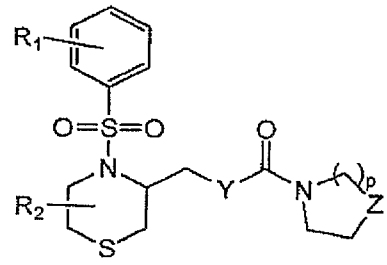
(ii) C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkoxy, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl and (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl; and

R_9 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl or (4- to 10-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl.

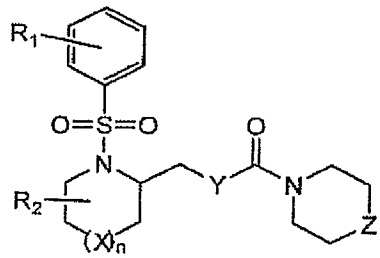
11. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:



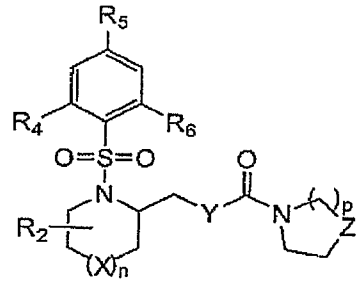
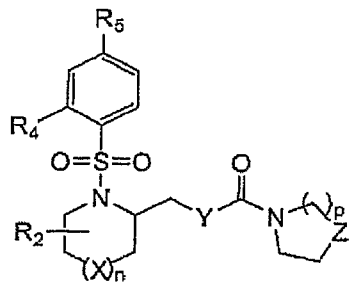
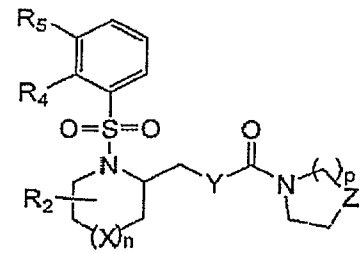
12. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:


,

or

.

13. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:

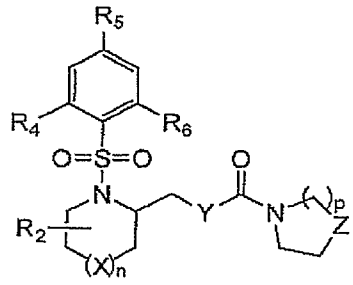

.

14. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:


,

or

;

wherein R_4, R_5 and R_6 are independently chosen from halogen, hydroxy, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy and C_1-C_6haloalkoxy.

15. A compound, salt or hydrate according to claim 14, wherein the compound has the formula:

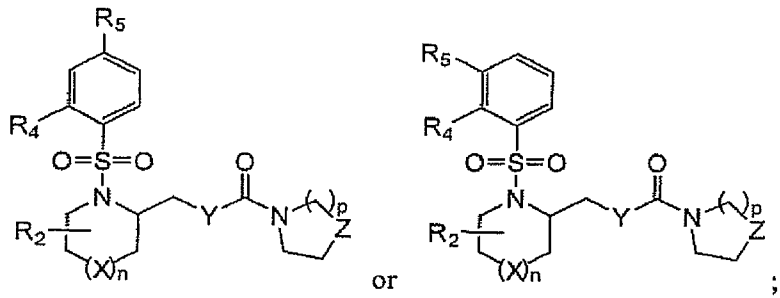


; and

(i) R_5 is methyl or methoxy, and R_4 and R_6 are each methyl; or

(ii) R_4 and R_6 each represent a halogen, and R_5 is a halogen, methoxy, trifluoromethyl or methyl.

16. A compound, salt or hydrate according to claim 14, wherein the compound has the formula:

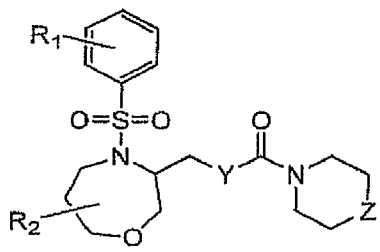


;

R_4 is a halogen; and

R_5 is a halogen, methoxy, trifluoromethyl or methyl.

17. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:



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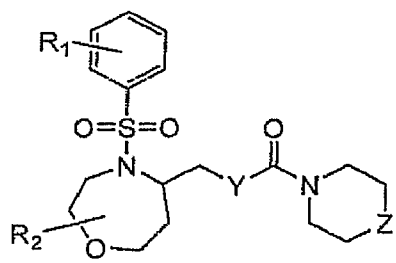
18. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:



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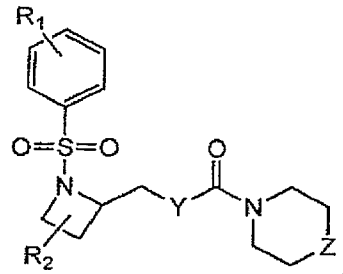
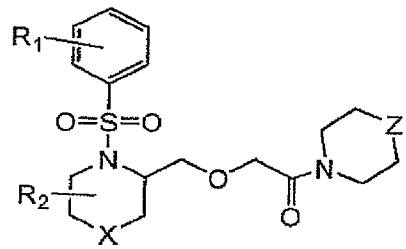
19. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:



20. A compound, salt or hydrate according to claim 11, wherein the compound satisfies the formula:



wherein:

Z is CR_7R_8 or NR_9;

R_7 is hydrogen, hydroxy, cyano or C_1-C_6alkyl; and

R_8 is C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl, phenylC_0-C_4alkyl or (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from hydroxy, halogen, oxo, cyano, C_1-C_4alkyl and C_1-C_4alkoxy; and

R_9 is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, (C_3-C_{10}carbocycle)C_0-C_4alkyl or (4- to 10-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl.

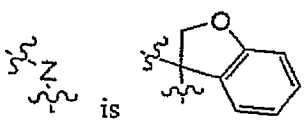
21. A compound, salt or hydrate according to any one of claims 10-20, wherein Z is CR_7R_8.

22. A compound, salt or hydrate according to claim 21, wherein:

R_7 is hydrogen, hydroxy, cyano or C_1-C_6alkyl; and

R_8 is mono- or di-(C_1-C_6alkyl)aminoC_0-C_4alkyl or (4- to 8-membered heterocycloalkyl)C_0-C_4alkyl that is optionally substituted with C_1-C_2alkyl.

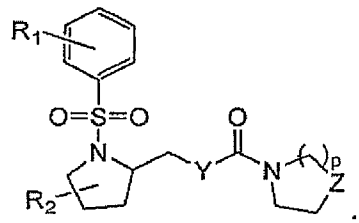
23. A compound, salt or hydrate according to claim 21, wherein:

 is .

24. A compound, salt or hydrate according to any one of claims 10-20, wherein Z is NR_9.

25. A compound, salt or hydrate according to claim 24, wherein R_9 is C_1-C_6alkyl, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl or (5- to 7-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 2 substituents independently chosen from halogen, hydroxy, cyano, oxo and C_1-C_6alkyl.

26. A compound, salt or hydrate according to claim 10, wherein the compound satisfies the formula:



27. A compound, salt or hydrate according to claim 1, wherein:

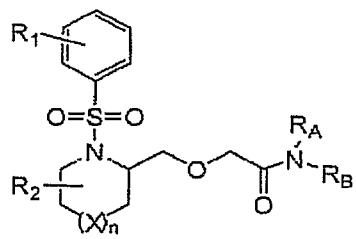
R_A is hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, or mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl; and

R_B is C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_2-C_6alkyl ether, mono- or di-(C_1-C_6alkyl)aminoC_1-C_4alkyl, or (5- or 6-membered heterocycloalkyl)C_0-C_4alkyl, each of which is substituted with from 0 to 6 substituents independently chosen from:

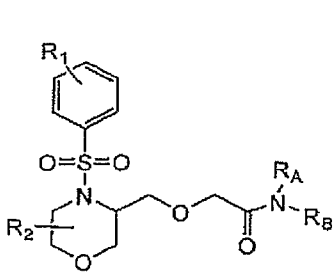
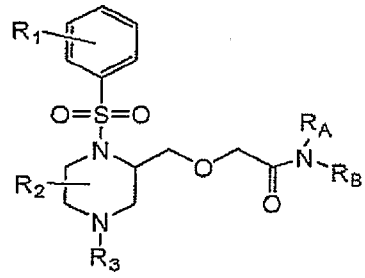
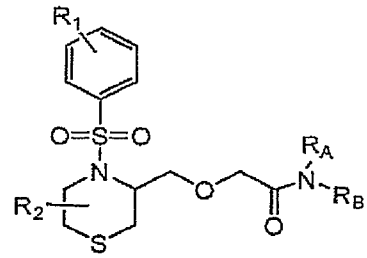
(i) amino, halogen, hydroxy, cyano and oxo; and

(ii) C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6alkoxy, phenylC_0-C_4alkyl and (5- or 6-membered heterocycle)C_0-C_4alkyl, each of which is substituted with from 0 to 4 substituents independently chosen from amino, cyano, halogen, hydroxy, C_1-C_6alkyl, (C_3-C_8cycloalkyl)C_0-C_4alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6alkoxycarbonyl, mono- or di-(C_1-C_6alkyl)amino, phenylC_0-C_4alkyl and phenylC_0-C_4alkoxy.

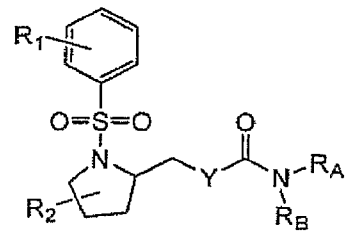
28. A compound, salt or hydrate according to claim 27, wherein the compound satisfies the formula:



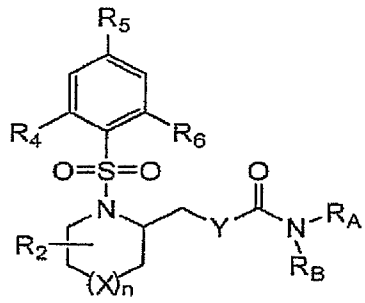
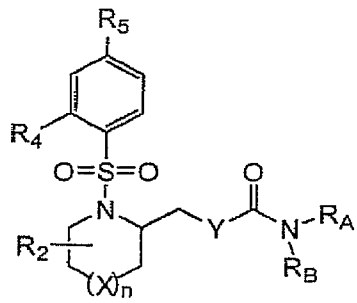
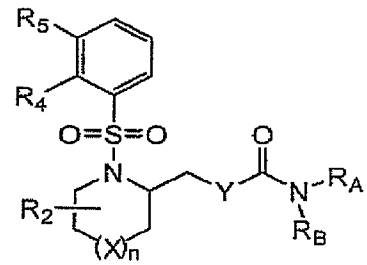
29. A compound, salt or hydrate according to claim 28, wherein the compound satisfies the formula:


,

or

.

30. A compound, salt or hydrate according to claim 27, wherein the compound satisfies the formula:


.

31. A compound, salt or hydrate according to claim 27, wherein the compound satisfies the formula:


,

or


wherein R_4, R_5 and R_6 are independently chosen from halogen, hydroxy, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy and C_1-C_6haloalkoxy.

32. A compound, salt or hydrate according to any one of claims 1-31, wherein the compound exhibits no detectable agonist activity an *in vitro* assay of B_1 agonism.

33. A compound, salt or hydrate according to any one of claims 1-32, wherein the compound has an IC_{50} value of 1 micromolar or less in an *in vitro* assay of B_1 antagonism.

34. A pharmaceutical composition, comprising at least one compound, salt or hydrate according to any one of claims 1-33, in combination with a physiologically acceptable carrier or excipient.

35. A pharmaceutical composition according to claim 34, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

36. A method for inhibiting induction of agonist-induced B_1 activity *in vitro*, the method comprising contacting B_1 receptor with at least one compound, salt or hydrate according to any one of claims 1-33, under conditions and in an amount sufficient to detectably inhibit agonist-induced B_1 activity.

37. A method for inhibiting induction of agonist-induced B_1 activity in a patient, comprising contacting cells expressing B_1 receptor with at least one compound, salt or hydrate according to any one of claims 1-332, in an amount sufficient to detectably inhibit agonist-induced B_1 activity in cells expressing a cloned B_1 receptor *in vitro*, and thereby inhibiting agonist-induced B_1 activity in the patient.

38. A method according to claim 37, wherein the patient is a human.

39. A method for treating a condition responsive to B_1 receptor modulation in a patient, comprising administering to the patient a therapeutically effective amount of at least one compound, salt or hydrate according to any one of claims 1-33, and thereby alleviating the condition in the patient.

40. A method according to claim 39, wherein the condition is inflammation or pain.

41. A method according to claim 39, wherein the condition is cough, asthma, vascular edema, or epilepsy.

42. A method for treating pain in a patient, comprising administering to a patient suffering from pain a therapeutically effective amount of at least one compound, salt or hydrate according to any one of claims 1-33, and thereby alleviating pain in the patient.

43. A method according to claim 42, wherein the patient is suffering from inflammatory pain, acute pain, dental pain, back pain, surgical pain, headache, neuropathic pain or pain from osteoarthritis or trauma.

44. A method according to claim 42, wherein the patient is a human.

45. A compound, salt or hydrate according to claim 1, wherein the compound, salt or hydrate is radiolabeled.

46. A method for determining the presence or absence of B_1 receptor in a sample, comprising the steps of:

(a) contacting a sample with a compound, salt or hydrate according to any one of claims 1-33, under conditions that permit binding of the compound to B_1 receptor; and

(b) detecting a signal indicative of a level of the compound bound to B_1 receptor, and therefrom determining the presence or absence of B_1 receptor in the sample.

47. A method according to claim 46, wherein the compound is a radiolabeled compound according to claim 43, and wherein the step of detection comprises the steps of:

(i) separating unbound compound from bound compound; and

(ii) detecting the presence or absence of bound radiolabel in the sample.

48. A packaged pharmaceutical preparation, comprising:

(a) a pharmaceutical composition according to claim 34 in a container; and

(b) instructions for using the composition to treat pain.

49. The use of a compound, salt or hydrate according to any one of claims 1-33 for the manufacture of a medicament for the treatment of a condition responsive to B_1 receptor modulation.

50. A use according to claim 49, wherein the condition is an inflammatory condition or pain.